Hepatic late adverse effects after antineoplastic treatment for childhood cancer

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[Intervention Review]

Hepatic late adverse effects after antineoplastic treatment for childhood cancer

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ABSTRACT

Background

Survival rates have greatly improved as a result of more effective treatments for childhood cancer. Unfortunately the improved prognosis has resulted in the occurrence of late, treatment-related complications. Liver complications are common during and soon after treatment for childhood cancer. However, among long-term childhood cancer survivors the risk of hepatic late adverse effects is largely unknown. To make informed decisions about future cancer treatment and follow-up policies it is important to know the risk of, and associated risk factors for, hepatic late adverse effects.

Objectives

To evaluate the existing evidence on the association between antineoplastic treatment for childhood cancer and hepatic late adverse effects.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2), MEDLINE (1966 to June 2009) and EMBASE (1980 to June 2009). In addition, we searched reference lists of relevant articles and conference proceedings.

Selection criteria

All studies except case reports, case series and studies including less than 10 patients that examined the association between antineoplastic treatment for childhood cancer (aged 18 years or less at diagnosis) and hepatic late adverse effects (one year or more after the end of treatment).

Data collection and analysis

Two review authors independently performed the study selection, risk of bias assessment and data extraction.

Main results

We identified 20 cohort studies investigating hepatic late adverse effects after antineoplastic treatment for childhood cancer. All studies had methodological limitations. The prevalence of hepatic late adverse effects varied widely, between 0% and 84.2%. Selecting studies where the outcome of hepatic late adverse effects was well defined as alanine aminotransferase (ALT) above the upper limit of normal resulted in five studies. In this subgroup the prevalence of hepatic late adverse effects ranged from 8.0% to 52.8%, with follow-up durations varying from one to 27 years after the end of treatment. A more stringent selection process using the outcome definition of ALT as above twice the upper limit of normal resulted in three studies, with a prevalence ranging from 7.9% to 44.8%. Chronic viral hepatitis was identified as a risk factor for hepatic late adverse effects in univariate analyses. It is unclear which specific antineoplastic treatments increase the risk of hepatic late adverse effects

Authors' conclusions

The prevalence of hepatic late adverse effects ranged from 7.9% to 52.8% when selecting studies with an adequate outcome definition. It has not been established which childhood cancer treatments result in hepatic late adverse effects. There is a suggestion that chronic viral hepatitis increases the risk of hepatic late adverse effects. More well-designed studies are needed to reliably evaluate the prevalence of, and risk factors for, hepatic late adverse effects after antineoplastic treatment for childhood cancer.

PLAIN LANGUAGE SUMMARY

Treatment-related late effects on the liver in survivors of childhood cancer

Advances in the treatment of childhood cancer over the last decades have greatly improved the survival rates. Unfortunately, the improved prognosis has been accompanied by the occurrence of late, treatment-related complications. One of the adverse effects that can occur due to treatment of childhood cancer is damage to the liver. Hepatic adverse effects are common both during and soon after treatment. However, the evidence on adverse effects in the liver many years after treatment is still inconclusive. Liver injury as a result of childhood cancer treatment is most often subclinical (asymptomatic). If liver disease becomes symptomatic, a person's complaints may include fatigue, jaundice, nausea, weight loss and abdominal pain. The development of future treatment and follow-up policies should be based on high quality evidence on the risk of, and associated risk factors for, hepatic late adverse effects.

In this systematic review, 20 cohort studies examining hepatic late adverse effects after antineoplastic treatment for childhood cancer were included. The authors found that 8% to 53% of the childhood cancer survivors developed hepatic late adverse effects after their treatment. It is unclear which childhood cancer treatments increase the risk of hepatic late adverse effects. Childhood cancer survivors with chronic viral hepatitis seemed to have an increased risk of hepatic late adverse effects. The quality of the evidence was however limited. Therefore, more high quality research is needed.

BACKGROUND

Survival rates have greatly improved as a result of more effective treatments for childhood cancer. Today, most children diagnosed with cancer are expected to become long-term cancer survivors (Curry 2006). Five-year disease-free survival now reaches 80% in Europe (Gatta 2009). Unfortunately, the improved prognosis has been accompanied by the occurrence of late, treatment-related complications. In two large cohort studies of childhood cancer survivors nearly 75% experienced one or more late adverse effects (Geenen 2007; Oeffinger 2006).

Liver complications are common during and soon after treatment for childhood cancer (Field 2008). However, among long-term childhood cancer survivors the prevalence of chronic liver disease, like fibrosis and cirrhosis, is largely unknown. It has been suggested that survivors of childhood cancer who received chemotherapy, particularly methotrexate, 6-mercaptopurine, 6-thiogua-

nine, busulphan and dactinomycin; bone marrow transplantation (BMT); radiotherapy involving the liver, including total body irradiation (TBI); or hepatectomy are at risk for developing hepatic late adverse effects (Bresters 2008; Castellino 2010; Dawson 2005; King 2001). However the evidence has been inconclusive.

The aetiology of chronic liver disease following treatment for childhood cancer is complex as often more than one aetiologic factor is present. In addition to cancer treatment, other causes of chronic liver disease are chronic viral hepatitis, veno-occlusive disease (VOD), graft-versus-host disease (GVHD), and iron overload (Locasciulli 1997; Rizzo 2006; Strasser 1999). Regarding chronic viral hepatitis, patients who were treated for childhood cancer before effective hepatitis C virus (HCV) donor screening was implemented are especially at risk for transfusion-acquired HCV infection. Childhood cancer survivors differ from other groups with chronic viral hepatitis in that they acquired the infection at a young age and were likely to have received immunosuppressive or hepatotoxic therapy (Fink 1993; Strickland 2000).

For better development of primary and secondary hepatic protective strategies in childhood cancer, more insight into the association between cancer treatment and hepatic late adverse effects is essential. Furthermore, for the follow-up of childhood cancer survivors it is crucial to know the risk and associated risk factors so that patients at greatest risk can be identified and adequate follow-up protocols established to reduce the consequences of hepatic late adverse effects. With increased survival duration after cancer, survivors are at risk for second malignancies and normal diseases of aging which will require additional pharmacotherapy. This additional morbidity risk also underscores the need for understanding the state of liver health in the long-term survivor of a childhood cancer.

OBJECTIVES

To evaluate all the existing evidence on the association between antineoplastic treatment (that is chemotherapy, radiotherapy involving the liver, surgery involving the liver and BMT) for childhood cancer and hepatic late adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

All study designs except case reports, case series (that is description of non-consecutive cases) and studies including less than 10 patients that examined the association between antineoplastic treatment for childhood cancer and hepatic late adverse effects.

Types of participants

Childhood cancer survivors, diagnosed between the age of 0 and 18 years, who were at least one year after the end of their cancer treatment. More than 50% of the study group should have been diagnosed between the age of 0 and 18 years. In addition, more than 50% of the study group should have been off treatment for at least one year. Because the aim of this systematic review was to evaluate the risk of, and associated risk factors for, hepatic late adverse effects after antineoplastic treatment for childhood cancer, we excluded studies in which the study population consisted solely of childhood cancer survivors with chronic viral hepatitis. In this way, it was possible to reliably evaluate risk factors for hepatic late adverse effects after cancer treatment.

Types of interventions

Treatment with chemotherapy, radiotherapy involving the liver (including TBI), surgery involving the liver or BMT, or both. Liver transplantations were excluded.

Types of outcome measures

Hepatic late adverse effects measured by liver enzymes (that is alanine aminotransferase (ALT), glutamic pyruvic transaminase (SGPT) and aspartate aminotransferase (AST), glutamic oxaloacetic transaminase (SGOT) to investigate cellular liver injury, and gamma-glutamyltransferase (GGT)) and alkaline phosphatase (ALP) or bilirubin, or both, to investigate disturbances in bile excretion and biliary tract injury. In addition, measures of liver synthetic function were included: coagulation times (prothrombin time (PTT) or activated partial thromboplastin time (APTT)), albumin or liver histology, or both. These clinically relevant outcome measures were selected as recommended by an expert in the field (BK). In this review we used the cut-off limit for normal and abnormal liver enzyme values as specified by the authors of the original studies.

Search methods for identification of studies

Electronic searches

The following electronic databases were searched: the Cochrane Central Library of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2), MEDLINE (PubMed) (from 1945 to June 2009) and EMBASE (Ovid) (from 1980 to June 2009). The sensitive search strategies used for MEDLINE, EMBASE and CENTRAL are presented in Appendix 1, Appendix 2 and Appendix 3.

Searching other resources

The reference lists of all relevant articles and reviews were screened for additional references which were not registered in MEDLINE, EMBASE or CENTRAL. We also scanned the conference proceedings of the International Society of Paediatric Oncology (SIOP) (from 2005 to 2009) electronically.
We did not impose language restrictions.

Data collection and analysis

Selection of studies

After performing the search strategy described previously, two review authors independently selected studies that met the inclusion criteria. Discrepancies between review authors were resolved by consensus. If this was impossible, we achieved final resolution using a third-party arbitrator. We obtained the full text of any study seemingly meeting the inclusion criteria on the grounds of the title or abstract, or both, for closer inspection. We clearly stated the details of our reasons for exclusion of any study considered for this review.

Data extraction and management

Two review authors independently performed data extraction using standardised forms. The following data were extracted: study design, original cohort, described study group, study group of interest, study group with liver function testing, control group (if applicable), patient characteristics (including age, gender, body mass index (BMI), tumour type, years of survival, acute liver disease and hepatitis virus infection), cancer treatment (including chemotherapy, radiotherapy involving the liver, BMT and hepatectomy), duration and completion of follow-up, hepatic late adverse effects (including method of detection, definition and outcome measure) and risk factors. In case of disagreement, a third review author was consulted.
We defined cohort studies as studies in which a group of consecutive patients treated for childhood cancer was followed from a similar well defined point in the course of the disease (x-year survivors). The described study group could be the entire original cohort of childhood cancer survivors or a subgroup of the original cohort, based on well defined inclusion criteria.
The patients in the original cohort represent the whole group of childhood cancer survivors. The described study group encompasses the childhood cancer survivors from the original cohort included in the study. The study group of interest are the childhood cancer survivors within the original cohort who received treatment with a high potential for hepatic late adverse effects. Finally, the study group with liver function testing are the childhood cancer survivors who were assessed for hepatic late adverse effects as well.

Assessment of risk of bias in included studies

The assessment of risk of bias was based on earlier described checklists for observational studies according to Evidence-Based Medicine Criteria (Grimes 2002; Laupacis 1994). Two review authors independently undertook the assessment of risk of bias of the included studies, concerning the selection of the study group, the follow-up and outcome assessments, and the methods used for risk estimation. For evaluation of internal validity we assessed the risk of selection bias, attrition bias, detection bias and confounding that was present in the included studies. It included the following items: representativeness of the study group, completeness of the follow-up, blinding of the outcome assessors, and adjustment for important confounding factors. For evaluation of external validity we assessed the risk of reporting bias, which included the following items: definition of the study group, reporting the length of follow-up, objectiveness of the outcome definition and definition of the analyses. The risk of bias assessment criteria for observational studies are described in additional Table 1. Discrepancies between review authors were resolved by consensus. In case of doubt, a third review author was consulted.

Measures of treatment effect

Prevalence, cumulative incidence, mean difference, relative risk, odds ratio, attributable risk, and other associated outcomes.

Assessment of heterogeneity

Heterogeneity was assessed both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, that is the I^2 statistic ($I^2 > 50\%$ was considered as substantial heterogeneity) (Higgins 2009). If there was evidence of substantial heterogeneity, this was reported.

Assessment of reporting biases

We planned to construct a funnel plot to graphically ascertain the existence of publication bias. A rule of thumb is that tests for funnel plot asymmetry are used only when there are at least 10 studies in the meta-analysis. In the event of less than 10 studies the power of the test is too low to distinguish chance from real asymmetry (Higgins 2009). Given that none of the included studies in the current analysis were pooled, we could not construct funnel plots.

Data synthesis

Data were entered into RevMan and analysed according to the guidelines of the Cochrane Handbook (Higgins 2009). We used a random-effects model throughout the review. All results are presented with the corresponding 95% confidence interval (95% CI). We used the generic inverse variance function of RevMan to combine the prevalences of hepatic late adverse effects. If pooling was not possible, we provided descriptive results of these studies.

Sensitivity analysis

We did not perform sensitivity analyses since pooling was not possible for any of the outcomes. We did take into account the risk of bias in studies included in this systematic review in the interpretation of the results. We excluded studies with a high risk of bias and studies for which the presence of bias was unclear to compare the studies with a low risk of bias with the results of all available studies.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

After performing the searches of the electronic databases of MEDLINE (PubMed), EMBASE (Ovid) and CENTRAL we identified 1703 references. Following initial screening of the titles and abstracts, or both, we excluded 1572 which clearly did not meet all pre-specified criteria for this systematic review. We obtained 131 articles in full text, of which seven met all the inclusion criteria. For an Icelandic article it was unclear if the study was eligible for inclusion. We are waiting for the translation. Therefore, this study was added to the Characteristics of studies awaiting classification table. The other 123 studies were not eligible for inclusion for the reasons described in the Characteristics of excluded studies table. After scanning the reference lists of relevant studies and reviews, 55 additional articles were retrieved for more detailed examination and of which 13 met all the inclusion criteria. Forty-two studies were added to the Characteristics of excluded studies table. By scanning the conference proceedings of SIOP, we identified two eligible studies that have not been published yet and are waiting for further assessment (see the Characteristics of studies awaiting classification table).

In total, our search identified 20 eligible studies examining the association between antineoplastic treatment for childhood cancer and hepatic late adverse effects. Characteristics of the included studies are summarised below and their baseline characteristics are described in the Characteristics of included studies table. It should be noted, however, that there might be partial overlap in included patients between the following studies: Locasciulli 1983, Locasciulli 1985, Locasciulli 1991a and Locasciulli 1997a; Guido 1991 and Rossetti 1991.

The total number of patients included in the 20 identified cohort studies who received treatment with a high potential for hepatic late adverse effects was 1590, ranging from 19 to 216 childhood cancer survivors per study. Thirteen studies included patients diagnosed with leukaemia (that is acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) and acute non-lymphoblastic leukaemia (ANLL)) (Aricò 1994; Bessho 1994; Chotsampancharoen 2009; Guido 1991; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Matsuzaki 2001; Ratner 1986; Rossetti 1991; Vora 2006; Weber 1987); two studies included patients with various forms of leukaemia and non-malignant disease (Frisk 1998; Locasciulli 1997a); one study with Wilms' tumour, neuroblastoma and hepatoblastoma (Tefft 1970); one study with hepatoblastoma (Stringer 1995); one study with various forms of leukaemia, benign haematological diseases, immunological diseases and other inborn errors (Bresters 2008); one study with Wilms' tumour (Jagt 2009); and one study with various tumours (Ballauff 1999).

In 19 of the 20 studies patients were treated with chemotherapy; in one study it was unclear whether the patients received chemotherapy (Chotsampancharoen 2009). In 16 studies the type of chemotherapy was mentioned, which varied considerably across the studies (Bessho 1994; Bresters 2008; Frisk 1998; Guido 1991; Jagt 2009; Locasciulli 1983; Locasciulli 1985; Locasciulli 1997b; Matsuzaki 2001; Ratner 1986; Rossetti 1991; Stringer 1995; Tefft 1970; Vora 2006; Weber 1987). Seven studies mentioned the chemotherapy dose according to the treatment protocol, which varied widely (Bessho 1994; Jagt 2009; Locasciulli 1997b; Matsuzaki 2001; Stringer 1995; Vora 2006; Weber 1987). For all but one study (Bessho 1994), the dose actually received by the patients was unclear. Seven of the 20 studies reported whether the patients were treated with radiotherapy involving the liver (Bresters 2008; Chotsampancharoen 2009; Frisk 1998; Locasciulli 1997b; Matsuzaki 2001; Stringer 1995; Tefft 1970) of which six studies included patients who received radiotherapy involving the liver (Bresters 2008; Chotsampancharoen 2009; Frisk 1998; Locasciulli 1997b; Stringer 1995; Tefft 1970). Four studies mentioned the radiotherapy field and dose, which varied from 7.5 to 14.4 Gy TBI (Chotsampancharoen 2009; Frisk 1998; Locasciulli 1997b) and from less than 25 Gy to more than 35 Gy liver irradiation (Tefft 1970). Two studies included patients treated with a hepatectomy (Stringer 1995; Tefft 1970). Moreover, five studies included patients treated with BMT (Bresters 2008; Chotsampancharoen 2009; Frisk 1998; Locasciulli 1991a; Locasciulli 1997b).

Eleven studies mentioned the age at diagnosis, which ranged from 0.0 to 19.0 years (Bessho 1994; Guido 1991; Jagt 2009; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Stringer 1995; Tefft 1970; Vora 2006; Weber 1987). The age at follow-up was reported by four studies (Aricò 1994; Ballauff 1999; Bessho 1994; Rossetti 1991) and ranged from 2.5 to 26.0 years. All but two studies (Ratner 1986; Vora 2006) mentioned the gender of the included patients. The percentage of females in these studies varied between 34% and 55%.

For the 18 studies that reported follow-up duration, the minimum and maximum duration varied widely from 0.0 to 13.0 years minimal and 4.0 to 27.0 years maximal after the end of treatment (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008;

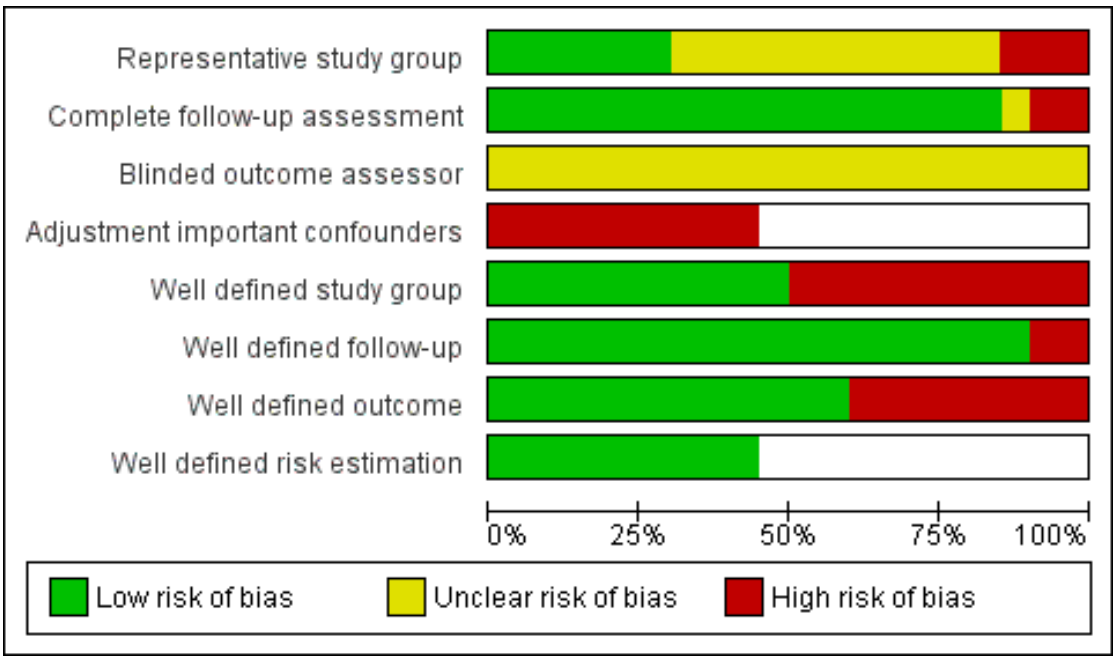
Chotsampancharoen 2009; Frisk 1998; Guido 1991; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Ratner 1986; Rossetti 1991; Stringer 1995; Tefft 1970; Vora 2006; Weber 1987). The median reported follow-up duration also showed variation, ranging from 2.0 to 17.0 years after the end of treatment.

In the included studies, hepatic late adverse effects were variably defined using ALT, AST, GGT, ALP, bilirubin and PTT. Fourteen studies defined hepatic late adverse effects by abnormal values of serum ALT or AST, or both (Aricò 1994; Bessho 1994; Bresters 2008; Chotsampancharoen 2009; Guido 1991; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Matsuzaki 2001; Ratner 1986; Rossetti 1991; Vora 2006); five studies defined hepatic late adverse effects by combined measurements of ALT, AST, bilirubin, GGT, ALP or PTT, or both (Ballauff 1999; Frisk 1998; Jagt 2009; Tefft 1970; Weber 1987); and for one study it was unclear which biochemical liver function tests were used (Stringer 1995). In 12 studies the upper limits of normal were described (Aricò 1994; Bessho 1994; Bresters 2008; Jagt 2009; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Ratner 1986; Rossetti 1991; Weber 1987): of which six studies defined hepatic late adverse effects as ALT or AST, or both, above the upper limit of normal (Aricò 1994; Bessho 1994; Bresters 2008; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b); three studies as ALT or AST, or both, above two times the upper limit of normal (Bresters 2008; Ratner 1986; Rossetti 1991); two studies as ALT or AST, or both, above three times the upper limit of normal (Locasciulli 1983; Locasciulli 1985); one study as ALT, AST, GGT and ALP above the upper limit of normal (Jagt 2009); and one study as ALT, bilirubin and ALP above the upper limit of normal (Weber 1987). In three studies liver biopsies were performed in a selected group of patients (Locasciulli 1997a; Ratner 1986; Vora 2006).

Risk of bias in included studies

Data on the risk of bias in the 20 cohort studies are described in the Characteristics of included studies table and are shown in Figure 1. All studies were found to have methodological limitations.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



For evaluation of internal validity we assessed the risk of selection bias, attrition bias, detection bias and confounding present in the included studies.

In five of the 20 studies the described study group consisted of the entire original cohort of childhood cancer survivors (Aricò 1994; Ballauff 1999; Frisk 1998; Locasciulli 1997b; Stringer 1995). Four studies described a subgroup of the original cohort (Bresters 2008; Chotsampancharoen 2009; Locasciulli 1991a; Locasciulli 1997a). In one study this subgroup consisted of more than 90% of the original cohort (Locasciulli 1997a). In the other three studies this subgroup neither consisted of more than 90% of the original cohort nor was it a random sample with respect to the cancer treatment (Bresters 2008; Chotsampancharoen 2009; Locasciulli 1991a). For 11 studies the number of patients in the original cohort was not mentioned (Bessho 1994; Guido 1991; Jagt 2009; Locasciulli 1983; Locasciulli 1985; Matsuzaki 2001; Ratner 1986; Rossetti 1991; Tefft 1970; Vora 2006; Weber 1987). For these studies it was unclear whether the described study group consisted of more than 90% of the original cohort of childhood cancer survivors or whether it was a random sample with respect to the cancer treatment. Hence, in six of the 20 studies (30.0%) the study group was representative. So, selection bias could not be ruled out in 70.0% of the included studies.

Seventeen studies (85.0%) had an adequate follow-up (based on > 60% of the study group of interest) (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; Frisk 1998; Jagt 2009; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Matsuzaki 2001; Ratner 1986; Rossetti 1991; Stringer 1995; Tefft 1970; Vora 2006; Weber 1987), of which 12 studies assessed the outcome for more than 90% of the study group of interest (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; Frisk 1998; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Ratner 1986; Stringer 1995; Vora 2006; Weber 1987). Two studies assessed the outcome for less than 60% of the study group of interest and thus were scored as having incomplete follow-up (Guido 1991; Locasciulli 1985), and for one study the completion of follow-up was unclear (Chotsampancharoen 2009). Hence, there was a risk of attrition bias in three of the 20 studies (15.0%).

Detection bias could not be ascertained as none of the studies reported that liver outcome was assessed by an investigator blinded to the treatment status of the participants.

Nine studies assessed possible risk factors for the development of hepatic late adverse effects (Aricò 1994; Ballauff 1999; Bresters 2008; Chotsampancharoen 2009; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Rossetti 1991; Tefft 1970). These studies only conducted univariate analyses and thus did not adjust for important confounders. So, there was a risk of confounding in 100% of the studies which assessed possible risk factors.

For evaluation of external validity we assessed the risk of reporting bias present in the included studies.

In 10 of the 20 studies (50.0%) the study group was well defined in terms of antineoplastic therapy exposure and chronic viral hepatitis (Bessho 1994; Bresters 2008; Frisk 1998; Guido 1991; Locasciulli 1983; Locasciulli 1985; Locasciulli 1997b; Matsuzaki 2001; Ratner 1986; Rossetti 1991). The other 10 studies failed to mention the type of chemotherapy (Aricò 1994; Ballauff 1999; Locasciulli 1991a; Locasciulli 1997a) or the number of participants with chronic viral hepatitis (Chotsampancharoen 2009; Jagt 2009; Stringer 1995; Tefft 1970; Vora 2006; Weber 1987).

Eighteen studies (90.0%) reported the length of follow-up and therefore had a well defined follow-up (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; Chotsampancharoen 2009; Frisk 1998; Guido 1991; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Ratner 1986; Rossetti 1991; Stringer 1995; Tefft 1970; Vora 2006; Weber 1987).

In 12 studies the upper limits of normal for the liver function tests that were used were described (Aricò 1994; Bessho 1994; Bresters 2008; Jagt 2009; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Ratner 1986; Rossetti 1991; Weber 1987). The other studies did not mention the upper limits of normal. So 12 of the 20 studies (60.0%) had a well defined outcome.

Nine studies assessed possible risk factors for the development of hepatic late adverse effects, all of which had a well defined risk estimation (100%) (Aricò 1994; Ballauff 1999; Bresters 2008; Chotsampancharoen 2009; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Rossetti 1991; Tefft 1970).

Hence, reporting bias could not be ruled out in up to 50.0% of the included studies.

Effects of interventions

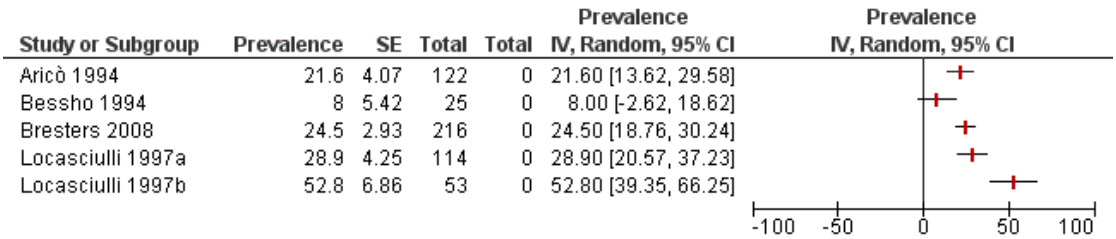
Prevalence of hepatic late adverse effects

The prevalence of hepatic late adverse effects as measured by liver enzymes, bilirubin or coagulation times was reported in all but one study (Chotsampancharoen 2009) and varied widely between 0% and 84.2% (see Characteristics of included studies). However, five studies estimated the prevalence of hepatic late adverse effects in a selected group of patients who were diagnosed with abnormal liver function during or soon after the cancer treatment (Guido 1991; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Vora 2006). Excluding these studies resulted in a reported prevalence of 0% to 58.0%.

Furthermore, hepatic late adverse effects were defined using different liver function tests with varying cut-off limits. When selecting studies with a well defined outcome, that is if the upper limits of normal for the liver function tests were described in the definition of hepatic late adverse effects, nine studies remained (Aricò 1994; Bessho 1994; Bresters 2008; Jagt 2009; Locasciulli 1997a; Locasciulli 1997b; Ratner 1986; Rossetti 1991; Weber 1987). Five studies defined hepatic late adverse effects as ALT above the upper limit of normal (Aricò 1994; Bessho 1994; Bresters 2008; Locasciulli 1997a; Locasciulli 1997b). The prevalence ranged from 8.0% to 52.8% (see Figure 2). Because unexplained heterogene-

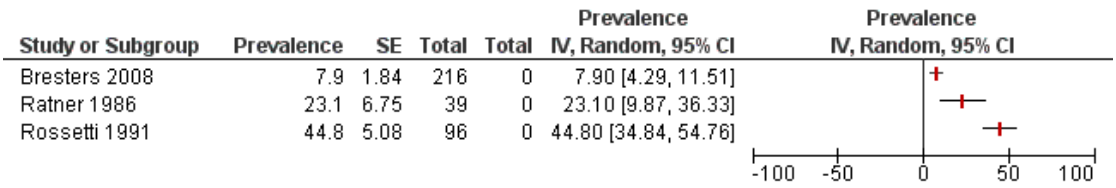
ity was detected (I^2 = 86%) we were not able to pool the results of these studies. The cancer treatment varied across the studies. In all five studies the included patients were treated with chemotherapy. The chemotherapy regimens varied considerably. In two studies it was reported that patients were also treated with TBI and BMT (Bresters 2008; Locasciulli 1997b). In these two studies the prevalence of hepatic late adverse effects was 24.5% and 52.8%, respectively. Selecting studies in which a considerable proportion of the patients had a chronic viral hepatitis resulted in three studies with a prevalence ranging from 21.6% to 52.8% (Aricò 1994; Locasciulli 1997a; Locasciulli 1997b). Although other potential sources of heterogeneity (that is risk of bias present in the studies, age at diagnosis, follow-up duration, gender, acute liver morbidity) also varied across these studies, they could not explain the variation in the prevalence of hepatic late adverse effects.

Figure 2. Forest plot of comparison: 1 Prevalence of hepatic late adverse effects, outcome: 1.1 Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above upper limit of normal.



Three studies defined hepatic late adverse effects as ALT above two times the upper limit of normal (Bresters 2008; Ratner 1986; Rossetti 1991). The prevalence ranged from 7.9% to 44.8% (see Figure 3). Heterogeneity was also detected in this analysis (I^2 = 96%). Patients included in the studies of Ratner 1986 (23.1%) and Rossetti 1991 (44.8%) received comparable chemotherapy regimens, that is vincristine, 6-mercaptopurine, methotrexate, asparaginase, cyclophosphamide, daunorubicin, hydroxyurea and asparaginase. The treatment received by patients included in the study of Bresters 2008 (7.9%) consisted of BMT, TBI, thoraco-abdominal irradiation (TAI), cyclophosphamide and busulphan. Chronic viral hepatitis could partly explain the variation in the prevalence reported in Rossetti 1991 (44.8%), Ratner 1986 (23.1%) and Bresters 2008 (7.9%) with infection rates of 62.5% (HBV), 12.8% (HBV) and 2.1% (HCV), respectively. In addition, the follow-up duration of patients included in the study of Rossetti 1991 was longer (4 to 20 years after diagnosis) than the follow-up duration in Ratner 1986 (1 to 8 years after the end of treatment) and Bresters 2008 (2 years after BMT). There were no differences in the risk of bias present in these studies.

Figure 3. Forest plot of comparison: 1 Prevalence of hepatic late adverse effects, outcome: 1.2 Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above twice upper limit of normal.



Because hepatic late adverse effects in the studies of Jagt 2009 and Weber 1987 were defined using different assessment methods, we were not able to combine the results of these two studies.

In three studies, liver biopsies were performed to evaluate hepatic late adverse effects in two, three and 10 patients, respectively (Locasciulli 1997a; Ratner 1986; Vora 2006). All liver biopsies were performed on clinical indication: persistent high ALT levels (Locasciulli 1997a), chronic HBV infection (Ratner 1986) and splenomegaly during and soon after chemotherapy (Vora 2006). Patients were diagnosed with either chronic persistent hepatitis, chronic lobular hepatitis, cirrhosis, portal fibrosis or nodular regenerative hyperplasia.

Risk factors for hepatic late adverse effects

Nine studies investigated possible risk factors for hepatic late adverse effects (Aricò 1994; Ballauff 1999; Bresters 2008; Chotsampancharoen 2009; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Rossetti 1991; Tefft 1970). Chronic viral hepatitis (HCV, HBV, HBV-HDV co-infection) (Aricò 1994; Ballauff 1999; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Rossetti 1991), older age at haematopoietic stem cell transplantation (HSCT), diagnosis of a benign haematological disease, gender, HSCT donor type (matched sibling donor, other), stem cell source, conditioning regimen (cyclophosphamide with total body irradiation (TBI) or thoraco-abdominal irradiation (TAI), cyclophosphamide with busulphan, other), early post-transplant morbidity (viral reactivation, VOD, acute GVHD) (Bresters 2008), higher radiotherapy dose, and radiotherapy field (right lobe, left lobe, entire liver, remaining liver) (Tefft 1970) were investigated as possible risk factors for hepatic late adverse effects in univariate analyses. There is a suggestion that chronic viral hepatitis increases the risk of hepatic late adverse effects. However, the identification of other risk factors has not been univocal across all studies (see Characteristics of included studies and additional Table 2).

DISCUSSION

In this review all available evidence on the association and risk of hepatic late adverse effects after treatment for childhood cancer was critically evaluated among 20 studies that met the inclusion criteria. The reported prevalence of hepatic late adverse effects varied considerably, between 0% and 84.2%. Part of this wide range could be explained by the variation in outcome definition. Selecting studies where the outcome of hepatic late adverse effects was well defined as ALT above the upper limit of normal resulted in five studies. In this subgroup the prevalence of hepatic late adverse effects ranged from 8.0% to 52.8%. A more stringent selection using an outcome definition of ALT above twice the upper limit of normal resulted in three studies, with a prevalence ranging from 7.9% to 44.8%. There is some suggestion that chronic viral hepatitis could explain a part of this variation. There is no clarity regarding which paediatric patients are at the greatest risk of developing hepatic late adverse effects since no study evaluated risk factors by multivariate analysis. However, there is a suggestion from univariate analyses that chronic viral hepatitis increases the risk of hepatic late adverse effects. The studies showed that even many years after the end of treatment (13 to 27 years) elevated liver transaminases, which indicate liver injury, were still detected. Since none of the studies investigated the longitudinal development of hepatic late adverse effects many years after treatment, it is unclear if liver function improves or deteriorates over time.

From previous research it is known that methotrexate, 6-mercaptopurine, 6-thioguanine, busulphan and dactinomycin increase the risk of liver toxicity during or soon after cancer treatment (Field 2008; King 2001). It has been speculative that these chemotherapeutics also increase the risk of hepatic late adverse effects. In the current systematic review, however, none of the included studies investigated the association between individual chemotherapeutic agents and hepatic late adverse effects. There was a great diversity in antineoplastic treatment among the participants in the individual studies, so it was impossible to compare the effects of specific chemotherapeutics from the included studies. Hence, despite the clear association between certain chemotherapeutic agents and acute transaminase elevation, veno-occlusive disease (VOD) and synthetic liver dysfunction (Field 2008; King 2001) the evidence

for an increased risk of hepatic late adverse effects after treatment with methotrexate, 6-mercaptopurine, 6-thioguanine, busulphan or dactinomycin is limited.

Moreover, only one included study investigated the association between radiotherapy to the liver and hepatic late adverse effects (Tefft 1970). The study found that 58% of the patients had abnormal liver function tests at a mean follow-up of four years after the end of treatment. The majority of patients were treated with a liver irradiation dose of 25 Gy or more. Studies investigating the association between radiotherapy to the liver and acute hepatotoxicity showed that the risk increased with radiation dose and volume, younger age at treatment and prior partial hepatectomy (Hudson 2005). Tefft 1970, however, did not show that a higher radiotherapy dose is a risk factor for hepatic late adverse effects.

Chronic HBV and HCV infection were identified in six studies as risk factors for hepatic late adverse effects, identified in univariate analyses only. Acute HBV infection in children has a variable clinical course ranging from asymptomatic state to fulminant hepatitis, with the rate of chronic infection ranging from 90% in neonates to 1% to 5% in adolescents (Kurbegov 2009). Acute infection with HCV tends to cause mild hepatitis, yet chronic infection occurs in approximately 80% of patients (Villano 1999). When chronically infected with HBV or HCV, patients are at risk for liver-related morbidity and mortality from cirrhosis or hepatocellular carcinoma. In a study of Castellino 2004, which investigated the long-term outcomes of chronic HCV infection among survivors of childhood cancer, it was shown that at a median follow-up of 12.4 years 28.8% of patients had developed mild fibrosis, 35.6% moderate fibrosis and 13.6% cirrhosis. This study was excluded from this systematic review because the study population consisted solely of hepatitis virus infected childhood cancer survivors. It should be noted, however, that the importance of chronic HCV infection among childhood cancer survivors is declining as the global prevalence of HCV has dramatically decreased since the introduction of effective screening of blood products in 1993 (Hudson 2005). Other reported risk factors were iron overload, older age at haematopoietic stem cell transplantation (HSCT) and the diagnosis of a benign haematological disease; although none of the studies conducted multivariate analyses with adjustment for important prognostic factors and follow-up. Results from univariate analyses that do not take possible confounding factors into account may lead to an overestimation of the prognostic influence of a single variable. Consequently, the results of these studies must be interpreted with caution. No studies exist in which the association between VOD or graft-versus-host disease (GVHD) and hepatic late adverse effects was evaluated. In addition, none of the studies in this systematic review included a control group. A control group would have allowed us to separate out the effects of important risk factors in order to determine the level of causation.

Liver histology is the current gold standard for diagnosing liver damage but is applied conservatively in paediatric patients due to the invasive nature of the test (Saleh 2007). Since only three studies performed liver biopsies, in a selected group of patients with clinical indications, we were not able to analyse histologically determined hepatic late adverse effects. Consequently, we had to focus on hepatic injury defined by elevated liver enzymes, especially serum ALT level. Although ALT is produced by other organs, it is found mainly in hepatocytes and is considered to be the most reliable and sensitive single marker of acute or subacute liver injury (Kim 2008). Recently Ruhl 2009 investigated whether elevated ALT levels were associated with an increased risk of all-cause and disease-specific mortality among 14,950 adults from the US population. Although elevated ALT was not associated with all-cause mortality, it did relate to deaths from liver disease. An elevation in ALT was associated with a more than eight-fold increased risk of cause-specific mortality from liver disease. There is, however, still some doubt about the validity of serum ALT as a marker of liver disease. Elevated ALT can be asymptomatic and does not always progress to liver failure or cirrhosis. Also, especially in the case of chronic HCV infection, normal ALT levels have been found while having mild liver abnormalities (Field 2008; Kim 2008). Therefore, it is difficult to judge the exact clinical consequence of hepatic late adverse effects as measured in this systematic review. Other parameters which are frequently used for liver function testing are ALP, GGT, bilirubin and coagulation times (PTT and APTT). Because the studies included in this systematic review mainly reported ALT levels it was impossible to draw any conclusions on other measures of liver function and their relation to long-term liver health in childhood cancer survivors.

After assessing the risk of bias of the included studies, which included both the internal and external validity, it was obvious that all studies had methodological limitations. However, it should be noted that this assessment focused only on the evaluation of the prevalence of hepatic late adverse effects. Therefore, the quality of the included studies was only judged regarding these items.

The internal validity gives an indication of the bias present in a study and thus how valid the results of a study are. There is a 70% risk of selection bias in studies included in this systematic review. This leads to concern that an overestimation of the prevalence of hepatic late adverse effects exists if patients with a higher risk profile were selected for the study, and an underestimation if patients with a lower risk profile were selected. In addition, the small risk of attrition bias (15%) may lead to an overestimation of the prevalence of hepatic late adverse effects if patients lost to follow-up are in better health than those still under medical surveillance. Conversely, it will lead to an underestimation if patients lost to follow-up are more likely to be suffering from hepatic late adverse effects, for example because they were more frequently unable to complete the follow-up schedule of the study. Finally, there is also a risk of detection bias. This can lead to an overestimation of the prevalence of hepatic late adverse effects since knowledge of prognostic factors can increase the possibility of classifying patients as

having hepatic late adverse effects. However, because the outcome is defined by absolute laboratory values and can be interpreted objectively, blinding of the outcome assessor is of less importance in this systematic review.

The external validity of a study indicates how well the results of the study could be extrapolated to individual patients. There is a moderate risk of reporting bias in studies included in this systematic review. Because the study group was not well defined in half of the included studies, and only a small majority used an objective and precise outcome definition, it is difficult to interpret the results correctly. Although most of the studies reported the length of follow-up, the minimum and maximum duration varied widely, from 0.0 to 13.0 years minimal and 4.0 to 27.0 years maximal after the end of treatment. With short follow-up, it is possible that the injury to the liver may be transient and reversible. With longer follow-up, more patients will be at risk for hepatic late adverse effects. However, it is not clear whether treatment-related increased risks of hepatic late adverse effects will continue to be raised with more prolonged follow-up, or that the risk will level off or even decrease at some point of time. Therefore, cautious interpretation of the results is needed when the study findings are related to individual patients.

Variation in the studies that evaluate the prevalence of hepatic late adverse effects could also be explained by other factors. Differences in the prevalence of hepatic late adverse effects could be a reflection of different risk profiles in the study population. Factors such as chemotherapy type and dose, co-treatment with other hepatotoxic drugs, age at diagnosis and age at follow-up varied considerably across the studies, which may explain the variation in the prevalence. Moreover, it should be noted that the prevalence of chronic HBV and HCV infection differ between countries and is based on the era of cancer diagnosis (Hudson 2005). In Mediterranean countries chronic viral hepatitis is more endemic (Baldo 2008) so patients who received blood transfusions in these countries were at higher risk for chronic HBV or HCV infections.

In conclusion, this systematic review showed that the prevalence of hepatic late adverse effects ranged from 7.9% to 52.8% when selecting studies with an adequate outcome definition. It has not been established which childhood cancer treatments result in hepatic late adverse effects since most studies had limited sample sizes (that is power) to evaluate the role of independent treatment-related risk factors by multivariate analysis. There is a suggestion that chronic viral hepatitis increases the risk of hepatic late adverse effects in childhood cancer survivors.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review shows that childhood cancer survivors are at risk for hepatic late adverse effects defined as ALT above the upper limit of normal. Evaluation of serum ALT level could be helpful to screen early for hepatic late adverse effects. Abnormalities should initiate additional evaluation and measurement to prevent any further damage. However, recommendations about the time interval of evaluation, groups of survivors in which evaluation should be performed and the importance of other tests cannot be made based on current evidence. To keep in mind, no evidence of effect does not mean evidence of no effect. As more data become available, clinicians will be able to make better-informed decisions regarding the treatment of future childhood cancer patients and to develop targeted follow-up programs for survivors. Since liver disease can be indolent, it seems rational that counselling should be provided regarding preventive behaviours like avoidance of alcohol, immunization against hepatitis A and B, and cautious use of alternative therapies that have a risk of liver injury.

Implications for research

All studies showed methodological limitations. This underscores the need for well-designed studies which reliably evaluate the prevalence of hepatic late adverse effects after antineoplastic treatment for childhood cancer in a prospective multicentre approach; and the influence of risk factors such as different chemotherapeutic drugs, chronic viral hepatitis, steatosis, VOD, iron overload and GVHD. Survivors of haematopoietic stem cell transplant are likely to be a highly vulnerable group that warrants study in this area as well. Since many of the studies are quite dated and the epidemiology of chronic viral hepatitis has changed, more current data is needed. Ideally, future studies should longitudinally evaluate liver health in all children treated for cancer. Follow-up should be long enough and complete with precise and uniform outcome definitions, including transaminases and synthetic indicators of liver function. The development of imaging modalities which may lead to non-invasive characterisation of the liver also hold promise for this population. While the cancer survivor has many end organ risks after therapy, it remains to be investigated whether the unique regenerative capacity of the liver obviates follow-up for hepatic late adverse effects or whether certain host or therapy exposures lead to threshold effects for late liver injury.

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REFERENCES

References to studies included in this review

Aricò 1994 *{published data only}*
Aricò M, Maggiore G, Silini E, Bono F, Vigano C, Cerino A, et al. Hepatitis C virus infection in children treated for acute lymphoblastic leukemia. *Blood* 1994;**84**:2919–22.

Ballauff 1999 *{published data only}*
Ballauff A, Krahe J, Jansen B, Ross RS, Roggendorf H, Havers W. Chronic liver disease after treatment of malignancies in children [Chronische Hepatopathien nach Behandlung maligner Erkrankungen bei Kindern]. *Klinische Pädiatrie* 1999;**211**:49–52.

Bessho 1994 *{published data only}*
Bessho F, Kinumaki H, Yokota S, Hayashi Y, Kobayashi M, Kamoshita S. Liver function studies in children with acute lymphocytic leukemia after cessation of therapy. *Medical and Pediatric Oncology* 1994;**23**:111–5.

Bresters 2008 *{published data only}*
Bresters D, Van Gils IC, Dekker FW, Lankester AC, Bredius RG, Schweizer JJ. Abnormal liver enzymes two years after haematopoietic stem cell transplantation in children: prevalence and risk factors. *Bone Marrow Transplantation* 2008;**41**:27–31.

Chotsampancharoen 2009 *{published data only}*
Chotsampancharoen T, Gan K, Kasow KA, Barfield RC, Hale GA, Leung W. Iron overload in survivors of childhood leukemia after allogeneic hematopoietic stem cell transplantation. *Pediatric Transplantation* 2009;**13**:348–52.

Frisk 1998 *{published data only}*
Frisk P, Lonnerholm G, Oberg G. Disease of the liver following bone marrow transplantation in children: incidence, clinical course and outcome in a long-term perspective. *Acta Paediatrica* 1998;**87**:579–83.

Guido 1991 *{published data only}*
Guido M, Rossetti F, Rugge M, Cesaro S, Aneloni V, Ninfo V, et al. Leukemia and liver disease in childhood: clinical and histological evaluation. *Tumori* 1991;**77**:319–22.

Jagt 2009 *{published data only}*
Jagt CT, Zuckermann M, Ten Kate F, Taminiau JA, Dijkgraaf MG, Heij H, at al. Veno-occlusive disease as a complication of preoperative chemotherapy for Wilms tumor: A clinico-pathological analysis. *Pediatric Blood and Cancer* 2009;**53**:1211–5.

Locasciulli 1983 *{published data only}*
Locasciulli A, Vergani GM, Uderzo C, Jean G, Cattaneo M, Vergani D, et al. Chronic liver disease in children with leukemia in long-term remission. *Cancer* 52;**1983**:1080–7.

Locasciulli 1985 *{published data only}*
Locasciulli A, Alberti A, Rossetti F, Santamaria M, Santoro N, Madon E, et al. Acute and chronic hepatitis in childhood leukemia: a multicentric study from the Italian Pediatric Cooperative Group for Therapy of Acute Leukemia (AIL-AIEOP). *Medical and Pediatric Oncology* 1985;**13**:203–6.

Locasciulli 1991a *{published data only}*
Locasciulli A, Gornati G, Tagger A, Ribero ML, Cavalletto D, Cavalletto L. Hepatitis C virus infection and chronic liver disease in children with leukemia in long-term remission. *Blood* 1991;**78**:1619–22.

Locasciulli 1997a *{published data only}*
Locasciulli A, Testa M, Pontisso P, Benvegnu L, Fraschini D, Corbetta A, et al. Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. *Blood* 1997;**90**:4628–33.

Locasciulli 1997b *{published data only}*
Locasciulli A, Testa M, Valsecchi MG, Vecchi L, Longoni D, Sparano P, et al. Morbidity and mortality due to liver disease in children undergoing allogeneic bone marrow transplantation: a 10-year prospective study. *Blood* 1997; **90**:3799–805.

Matsuzaki 2001 *{published data only}*
Matsuzaki A, Ishii E, Nagatoshi Y, Eguchi H, Koga H, Yanai F, et al. Long-term outcome of treatment with protocols AL841, AL851, and ALHR88 in children with acute lymphoblastic leukemia: results obtained by the Kyushu-Yamaguchi Children's Cancer Study Group. *International Journal of Hematology* 2001;**73**:369–77.

Ratner 1986 *{published data only}*
Ratner L, Peylan-Ramu N, Wesley R, Poplack DG. Adverse prognostic influence of hepatitis B virus infection in acute lymphoblastic leukemia. *Cancer* 1986;**58**:1096–100.

Rossetti 1991 *{published data only}*
Rossetti F, Zancan L, Bonato MG, Quaranta E, Rosolen A, Rugge M, et al. Delta virus and childhood leukemia. *Pediatric Hematology and Oncology* 1991;**8**:23–32.

Stringer 1995 *{published data only}*
Stringer MD, Hennayake S, Howard ER, Spitz L, Shafford EA, Mieli-Vergani G, et al. Improved outcome for children with hepatoblastoma. *British Journal of Surgery* 1995;**82**: 386–91.

Tefft 1970 *{published data only}*
Tefft M, Mitus A, Das L, Vawter GF, Filler RM. Irradiation of the liver in children: review of experience in the acute and chronic phases, and in the intact normal and partially resected. *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* 1970;**108**:365–85.

Vora 2006 *{published data only}*
Vora A, Mitchell CD, Lennard L, Eden TO, Kinsey SE, Lilleyman J. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006;**368**:1339–48.

Weber 1987 *{published data only}*
Weber BL, Tanyer G, Poplack DG, Reaman GH, Feusner JH, Miser JS, at al. Transient acute hepatotoxicity of high-dose methotrexate therapy during childhood. *NCI Monographs: a publication of the National Cancer Institute* 1987;**5**:207–12.

References to studies excluded from this review

Adson 1981 *{published data only}*
Adson MA, Weiland LH. Resection of primary solid hepatic tumors. *American Journal of Surgery* 1981;**141**:18–21.

Al-Attar 1986 *{published data only}*
Al-Attar A, Pritchard J, Al-Saleem T. Intensive chemotherapy for non-localised Burkitt's lymphoma. *Archives of Disease in Childhood* 1986;**61**:1013–9.

Amylon 1997 *{published data only}*
Amylon MD, Co JPT, Snyder DS, Donaldson SS, Blume KG, Forman SJ. Allogeneic bone marrow transplant in pediatric patients with high-risk hematopoietic malignancies early in the course of their disease. *Journal of Pediatric Hematology/Oncology* 1997;**19**:54–61.

Atay 2005 *{published data only}*
Atay AA, Kurekci AE, Kesik V, Kilic S, Gulgun M, Ozcan O, et al. Retrospective analysis of children with acute lymphoblastic leukemia [Akut lenfoblastik losemili olgularimizin retrospektif analizi]. *Gulhane Medical Journal* 2005;**47**:183–6.

Avet Loiseau 1991 *{published data only}*
Avet Loiseau H, Hartmann O, Valteau D, McDowell H, Brugieres L, Vassal G, et al. High-dose chemotherapy containing busulfan followed by bone marrow transplantation in 24 children with refractory or relapsed non-Hodgkin's lymphoma. *Bone Marrow Transplantation* 1991;**8**:465–72.

Bacigalupo 1991 *{published data only}*
Bacigalupo A, Van Lint MT, Occhini D, Gualandi F, Lamparelli T, Sogno G, et al. Increased risk of leukemia relapse with high-dose cyclosporine A after allogeneic marrow transplantation for acute leukemia. *Blood* 1991;**77**: 1423–8.

Balcerska 2000 *{published data only}*
Balcerska A, Aleszewicz-Baranowska J, Adamkiewicz-Drozynska E, Bien E, Sierota D, Kaczorowska B, et al. Cardiotoxic complications in Wilms' tumour survivors after treatment with anthracyclines [Powiklania kardiotoksyczne u pacjentow z guzem wilmsa leczonych antracyklinami]. *Medycyna Wieku Rozwojowego* 2000;**4**:111–9.

Bauditz 2007 *{published data only}*
Bauditz J, Lochs H, Ventz M. Long-term follow-up of patients with suprasellar germinomas [Langzeitverlauf bei Patienten mit supraselläre Germinomen]. *Medizinische Klinik* 2007;**102**:803–8.

Benesch 2001 *{published data only}*
Benesch M, Lackner H, Moser A, Kerbl R, Schwinger W, Oberbauer R, et al. Outcome and long-term side effects after synchronous radiochemotherapy for childhood brain stem gliomas. *Pediatric Neurosurgery* 2001;**35**:173–80.

Berjian 1980 *{published data only}*
Berjian RA, Douglass HO Jr, Nava HR, Karakousis C. The role of hepatic artery ligation and dearterialization with infusion chemotherapy in advanced malignancies in the liver. *Journal of Surgical Oncology* 1980;**14**:379–87.

Berman 1980 *{published data only}*
Berman MM, Libbey NP, Foster JH. Hepatocellular carcinoma. Polygonal cell type with fibrous stroma--an atypical variant with a favorable prognosis. *Cancer* 1980; **46**:1448–55.

Bernstein 1993 *{published data only}*
Bernstein D, Baum D, Berry G, Dahl G, Weiss L, Starnes VA, et al. Neoplastic disorders after pediatric heart transplantation. *Circulation* 1993;**88**:230–7.

Blum 2002 *{published data only}*
Blum W, Brown R, Lin HS, Zehnbauer B, Khoury H, Goodnough LT, et al. Low-dose (550 cGy), single-exposure total body irradiation and cyclophosphamide: Consistent, durable engraftment of related-donor peripheral blood stem cells with low treatment-related mortality and fatal organ toxicity. *Biology of Blood and Marrow Transplantation* 2002; **8**:608–18.

Broxson 2005 *{published data only}*
Broxson EH, Dole M, Wong R, Laya BF, Stork L. Portal hypertension develops in a subset of children with standard risk acute lymphoblastic leukemia treated with oral 6-thioguanine during maintenance therapy. *Pediatric Blood and Cancer* 2005;**44**:226–31.

Brunet 2001 *{published data only}*
Brunet S, Urbano-Ispizua A, Ojeda E, Ruiz D, Moraleda JM, Diaz MA, et al. Favourable effect of the combination of acute and chronic graft-versus-host disease on the outcome of allogeneic peripheral blood stem cell transplantation for advanced haematological malignancies. *British Journal of Haematology* 2001;**114**:544–50.

Carter 1997 *{published data only}*
Carter TL, Cole CH, Mews CF, Price PJ, Baker DL. The prevalence of hepatitis C in survivors of paediatric malignancy. *Journal of Paediatrics and Child Health* 1997; **33**:238–41.

Cassady 1979 *{published data only}*
Cassady JR, Carabell SC, Jaffe N. Chemotherapy-irradiation related hepatic dysfunction in patients with Wilms' tumor. *Frontiers of Radiation Therapy and Oncology* 1979;**13**: 147–60.

Cavo 1998 *{published data only}*
Cavo M, Bandini G, Benni M, Gozzetti A, Ronconi S, Rosti G, et al. High-dose busulfan and cyclophosphamide are an effective conditioning regimen for allogeneic bone marrow transplantation in chemosensitive multiple myeloma. *Bone Marrow Transplantation* 1998;**22**:27–32.

Cesaro 1997 *{published data only}*
Cesaro S, Petris MG, Rossetti F, Cusinato R, Pipan C, Guido M, et al. Chronic hepatitis C virus infection after treatment for pediatric malignancy. *Blood* 1997;**90**: 1315–20.

Chao 1993 *{published data only}*
Chao NJ, Stein AS, Long GD, Negrin RS, Amylon MD, Wong RM, et al. Busulfan/etoposide - Initial experience with a new preparatory regimen for autologous bone marrow

transplantation in patients with acute nonlymphoblastic leukemia. *Blood* 1993;**81**:319–23.

Cheng 2005 *{published data only}*
Cheng HY, Chu CH, Chang WH, Hsu TC, Lin SC, Liu CC, et al. Clinical analysis of multiple primary malignancies in the digestive system: A hospital-based study. *World Journal of Gastroenterology* 2005;**11**:4215–9.

Cheuk 2008 *{published data only}*
Cheuk DK, Lee TL, Chiang AK, Ha SY, Chan GC. Autologous hematopoietic stem cell transplantation for high-risk brain tumors in children. *Journal of Neuro-Oncology* 2008;**86**:337–47.

Chou 1996 *{published data only}*
Chou RH, Wong GB, Kramer JH, Wara DW, Matthay KK, Crittenden MR, et al. Toxicities of total-body irradiation for pediatric bone marrow transplantation. *International Journal of Radiation Oncology, Biology, Physics* 1996;**34**: 843–51.

Christosova 2005 *{published data only}*
Christosova I, Velev M, Starbanov I, Bobev D, Konstantinov D, Brancov O. Hepatoblastoma - Treatment results. *Pediatriya* 2005;**45**:62–3.

Claviez 1996 *{published data only}*
Claviez A, Hero B, Schneppenheim R, Berthold F. Hepatopathy in patients with stage 4S neuroblastoma [Hepatopathie bei Patienten mit Neuroblastom Stadium 4S]. *Klinische Pädiatrie* 1996;**208**:221–8.

Colsky 1955 *{published data only}*
Colsky J, Greenspan EM, Warren TN. Hepatic fibrosis in children with acute leukemia after therapy with folic acid antagonists. *A.M.A. Archives of Pathology* 1955;**59**: 198–206.

Condren 2005 *{published data only}*
Condren M, Lubsch L, Vats TS. Long-term follow-up of survivors of childhood cancer. *Indian Journal of Pediatrics* 2005;**72**:39–43.

Damon 2006 *{published data only}*
Damon L, Rugo H, Tolaney S, Navarro W, Martin IT, Ries C, et al. Cytoreduction of lymphoid malignancies and mobilization of blood hematopoietic progenitor cells with high doses of cyclophosphamide and etoposide plus filgrastim. *Biology of Blood and Marrow Transplantation* 2006;**12**:316–24.

Deeg 1986 *{published data only}*
Deeg HJ, Sullivan KM, Buckner CD, Storb R, Appelbaum FR, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission: toxicity and long-term follow-up of patients conditioned with single dose or fractionated total body irradiation. *Bone Marrow Transplantation* 1986;**1**:151–7.

Dibenedetto 1994 *{published data only}*
Dibenedetto SP, Ragusa R, Sciacca A, Di Cataldo A, Miraglia V, D'Amico S, et al. Incidence and morbidity of infection by hepatitis C virus in children with acute lymphoblastic leukaemia. *European Journal of Pediatrics* 1994;**153**:271–5.

Dunkel 1998 *{published data only}*
Dunkel IJ, Boyett JM, Yates A, Rosenblum M, Garvin JH Jr, Bostrom BC, et al. High-dose carboplatin, thiotepa, and etoposide with autologous stem- cell rescue for patients with recurrent medulloblastoma. *Journal of Clinical Oncology* 1998;**16**:222–8.

Dupuis-Girod 1996 *{published data only}*
Dupuis-Girod S, Hartmann O, Benhamou E, Doz F, Mechinaud F, Bouffet E, et al. Will high dose chemotherapy followed by autologous bone marrow transplantation supplant cranio-spinal irradiation in young children treated for medulloblastoma?. *Journal of Neuro-Oncology* 1996;**27**: 87–98.

Evans 1980 *{published data only}*
Evans AE, Chatten J, D'Angio GJ, Gerson JM, Robinson J, Schnaufer L. A review of 17 IV-S neuroblastoma patients at the children's hospital of philadelphia. *Cancer* 1980;**45**: 833–9.

Evans 1982 *{published data only}*
Evans AE, Land VJ, Newton WA, Randolph JG, Sather HN, Tefft M. Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. *Cancer* 1982;**50**:821–6.

Evans 1990 *{published data only}*
Evans RG, Kimler BF, Morantz RA, Vats TS, Gemer LS, Liston V, et al. A phase I/II study of the use of Fluosol as an adjuvant to radiation therapy in the treatment of primary high-grade brain tumors. *International Journal of Radiation Oncology, Biology, Physics* 1990;**19**:415–20.

Evans 1993 *{published data only}*
Evans RG, Kimler BF, Morantz RA, Batnitzky S. Lack of complications in long-term survivors after treatment with Fluosol(R) and oxygen as an adjuvant to radiation therapy for high-grade brain tumors. *International Journal of Radiation Oncology, Biology, Physics* 1993;**26**:649–52.

Exelby 1975 *{published data only}*
Exelby PR, Filler RM, Grosfeld JL. Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey--1974. *Journal of Pediatric Surgery* 1975;**10**:329–37.

Fabbri 1994 *{published data only}*
Fabbri A, Motta E, Ferrari S, Longhi C, Marchi E, Bacci G, et al. High-dose methotrexate treatment and liver function in patients with osteosarcoma. *Journal of Internal Medicine* 1994;**236**:209–14.

Farthing 1982 *{published data only}*
Farthing MJ, Clark ML, Sloane JP, Powles RL, McElwain TJ. Liver disease after bone marrow transplantation. *Gut* 1982;**23**:465–74.

Fink 1993 *{published data only}*
Fink FM, Hocker-Schulz S, Mor W, Puchhammer-Stockl E, Hofmann H, Zoubek A, et al. Association of hepatitis C virus infection with chronic liver disease in paediatric cancer patients. *European Journal of Pediatrics* 1993;**152**:490–2.

Forbes 1995 *{published data only}*
Forbes GM, Davies JM, Herrmann RP, Collins BJ. Liver disease complication bone marrow transplantation: A clinical audit. *Journal of Gastroenterology and Hepatology* 1995;**10**:1–7.

Frickhofen 1994 *{published data only}*
Frickhofen N, Wiesneth M, Jainta C, Hertenstein B, Heymer B, Bianchi L, et al. Hepatitis C virus infection is a risk factor for liver failure from veno-occlusive disease after bone marrow transplantation. *Blood* 1994;**83**:1998–2004.

Gandola 2009 *{published data only}*
Gandola L, Massimino M, Cefalo G, Solero C, Spreafico F, Pecori E, et al. Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma. *Journal of Clinical Oncology* 2009;**27**:566–71.

Ganjoo 2006 *{published data only}*
Ganjoo K, An C, Robertson M, Gordon L, Sen J, Weisenbach J, et al. Rituximab, Bevacizumab and CHOP (RA-CHOP) in untreated diffuse large B-cell lymphoma: Safety, biomarker and pharmacokinetic analysis. *Leukemia and Lymphoma* 2006;**47**:998–1005.

Glick 2000 *{published data only}*
Glick RD, Nadler EP, Blumgart LH, La Quaglia MP. Extended left hepatectomy (left hepatic trisegmentectomy) in childhood. *Journal of Pediatric Surgery* 2000;**35**:303–7.

Gluckman 1979 *{published data only}*
Gluckman E, Devergie A, Dutreix A, Dutreix J, Boiron M, Bernard J. Total body irradiation in bone marrow transplantation. Hopital Saint-Louis results. *Pathologie et Biologie* 1979;**27**:349–52.

Gonzalez-Crussi 1982 *{published data only}*
Gonzalez-Crussi F, Upton MP, Maurer HS. Hepatoblastoma. Attempt at characterization of histologic subtypes. *The American Journal of Surgical Pathology* 1982;**6**:599–612.

Greenfield 2006 *{published data only}*
Greenfield DM, Wright J, Brown JE, Hancock BW, Davies HA, O'Toole L, et al. High incidence of late effects found in Hodgkin's lymphoma survivors, following recall for breast cancer screening. *British Journal of Cancer* 2006;**94**:469–72.

Grill 1996 *{published data only}*
Grill J, Kalifa C, Doz F, Schoepfer C, Sainte-Rose C, Couanet D, et al. A high-dose busulfan-thiotepa combination followed by autologous bone marrow transplantation in childhood recurrent ependymoma. A phase-II study. *Pediatric Neurosurgery* 1996;**25**:7–12.

Grosfeld 1976 *{published data only}*
Grosfeld JL, Fitzgerald JF, Wagner VM, Newton WA, Baehner RL. Portal hypertension in infants and children with histiocytosis X. *The American Journal of Surgery* 1976; **131**:108–13.

Gutjahr 1980 *{published data only}*
Gutjahr P. The condition of long-term survivors and patients cured of childhood neoplasms [Langzeit–Uberlebenden und Geheilter nach bosartigen Neubildungen im Kindesalter]. *Fortschritte der Medizin* 1980;**98**:289–92.

Haddy 1998 *{published data only}*
Haddy TB, Adde MA, McCalla J, Domanski MJ, Datiles M, Meehan SC, et al. Late effects in long-term survivors of high-grade non-Hodgkin's lymphomas. *Journal of Clinical Oncology* 1998;**16**:2070–9.

Hadley 2002 *{published data only}*
Hadley GP, Govender D, Landers G. Malignant solid tumours in neonates: An African perspective. *Pediatric Surgery International* 2002;**18**:653–7.

Halonen 2003 *{published data only}*
Halonen P, Mattila J, Ruuska T, Salo MK, Mäkipernaa A. Liver histology after current intensified therapy for childhood acute lymphoblastic leukemia: Microvesicular fatty change and siderosis are the main findings. *Medical and Pediatric Oncology* 2003;**40**:148–54.

Hanks 1980 *{published data only}*
Hanks JB, Meyers WC, Filston HC, Killenberg PG, Jones RS. Surgical resection for benign and malignant liver disease. *Annals of Surgery* 1980;**191**:584–92.

Harrison 1996 *{published data only}*
Harrison P, Neilson JR, Marwah SS, Madden L, Bareford D, Milligan DW. Role of non-transferrin bound iron in iron overload and liver dysfunction in long term survivors of acute leukaemia and bone marrow transplantation. *Journal of Clinical Pathology* 1996;**49**:853–6.

Hatanaka 1994 *{published data only}*
Hatanaka H, Nakagawa Y. Clinical results of long-surviving brain tumor patients who underwent boron neutron capture therapy. *International Journal of Radiation Oncology, Biology, Physics* 1994;**28**:1061–6.

Haupt 2004 *{published data only}*
Haupt R, Nanduri V, Calevo MG, Bernstrand C, Braier JL, Broadbent V, et al. Permanent consequences in Langerhans cell histiocytosis patients: A pilot study from the Histiocyte Society - Late Effects Study Group. *Pediatric Blood and Cancer* 2004;**42**:438–44.

Hedrick 2004 *{published data only}*
Hedrick HL, Flake AW, Crombleholme TM, Howell LJ, Johnson MP, Wilson RD, et al. Sacrococcygeal teratoma: Prenatal assessment, fetal intervention, and outcome. *Journal of Pediatric Surgery* 2004;**39**:430–8.

Hegewald 1982 *{published data only}*
Hegewald G, Reddemann H, Barenwald G, Schwanengel H. Electron microscopic findings in the livers of long-term survivors among child tumor patients after polychemotherapy [Elektronenmikroskopische Leberfunde bei langzeitüberlebenden Tumorpatienten im Kindesalter nach Polychemotherapie]. *Archiv für Geschwulstforschung* 1982;**52**:397–405.

Henderson 2008 *{published data only}*
Henderson T, Levine J, Patel S, Oeffinger KC. A risk-based approach to the care of survivors of childhood cancer: 3 Case studies. *Consultant* 2008;**48**:443–5.

Hjern 2007 *{published data only}*
Hjern A, Lindblad F, Boman KK. Disability in adult survivors of childhood cancer: A Swedish national cohort study. *Journal of Clinical Oncology* 2007;**25**:5262–6.

Ho 2004 *{published data only}*
Ho GT, Parker A, MacKenzie JF, Morris AJ, Stanley AJ. Abnormal liver function tests following bone marrow transplantation: aetiology and role of liver biopsy. *European Journal of Gastroenterology and Hepatology* 2004;**16**:157–62.

Hollard 1980 *{published data only}*
Hollard D, Sotto JJ, Berthier R, Leger J, Michallet M. High rate of long-term survivals in AML treated by chemotherapy and androgenotherapy: a pilot study. *Cancer* 1980;**45**: 1540–8.

Holschneider 1977 *{published data only}*
Holschneider AM, Geiger H, Bolkenius N, Janka G, Lampert F. Neuroblastoma: paraneoplastic diseases and late complications. *Monatsschrift fur Kinderheilkunde* 1977;**125**: 69–73.

Horowitz 1993 *{published data only}*
Horowitz ME, Kinsella TJ, Wexler LH, Belasco J, Triche T, Tsokos M, et al. Total-body irradiation and autologous bone marrow transplant in the treatment of high-risk Ewing's sarcoma and rhabdomyosarcoma. *Journal of Clinical Oncology* 1993;**11**:1911–8.

Hutter 1960 *{published data only}*
Hutter RVP, Shipkey FH, Tan CTC, Murphy ML, Chowdhury M. Hepatic fibrosis in children with acute leukemia: A complication of therapy. *Cancer* 1960;**13**: 288–307.

Ingold 1965 *{published data only}*
Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* 1965;**93**:200–208.

Isaacs 2008 *{published data only}*
Isaacs H Jr. Fetal hydrops associated with tumors. *American Journal of Perinatology* 2008;**25**:43–68.

Ivantes 2004 *{published data only}*
Ivantes CAP, Amarante H, Ioshii SO, Pasquini R. Hepatitis C virus in long-term bone marrow transplant survivors. *Bone Marrow Transplantation* 2004;**33**:1181–5.

Jaffe 1975 *{published data only}*
Jaffe N. Non-oncogenic sequelae of cancer chemotherapy. *Radiology* 1975;**114**:167–73.

Jagannathan 2004 *{published data only}*
Jagannathan J, Petit JH, Balsara K, Hudes R, Chin LS. Long-term survival after gamma knife radiosurgery for primary and metastatic brain tumors. *American Journal of Clinical Oncology: Cancer Clinical Trials* 2004;**27**:441–4.

Jirtle 1990 *{published data only}*
Jirtle RL, Anscher MS, Alati T. Radiation sensitivity of the liver. *Advances in Radiation Biology* 1990;**14**:269–311.

Kamani 1996 *{published data only}*
Kamani N, August CS, Bunin N, Leahey A, Bayever E, Goldwein J, et al. A study of thiotepa, etoposide and fractionated total body irradiation as a preparative regimen prior to bone marrow transplantation for poor prognosis patients with neuroblastoma. *Bone Marrow Transplantation* 1996;**17**:911–6.

Kamble 2006 *{published data only}*
Kamble R, Mims M. Iron-overload in long-term survivors of hematopoietic transplantation. *Bone Marrow Transplantation* 2006;**37**:805–6.

Kaste 1999 *{published data only}*
Kaste SC, Gronemeyer SA, Hoffer FA, Mandrell BN, Wilimas JA. Pilot study of noninvasive detection of venous occlusions from central venous access devices in children treated for acute lymphoblastic leukemia. *Pediatric Radiology* 1999;**29**:570–4.

Kazanowska 2004 *{published data only}*
Kazanowska B, Reich A, Reich M, Balcerska A, Balwierz W, Bodalski J, et al. Remaining problems and controversies in the management of childhood head and neck soft tissue sarcomas: Retrospective (national) multicenter study of the Polish Pediatric Solid Tumors Group. *Pediatric Hematology and Oncology* 2004;**21**:349–62.

Khouri 2002 *{published data only}*
Khouri IF, Keating MJ, Saliba RM, Champlin RE. Long-term follow-up of patients with CLL treated with allogeneic hematopoietic transplantation. *Cytotherapy* 2002;**4**:217–21.

Kim 2000 *{published data only}*
Kim BK, Chung KW, Sun HS, Min WS, Kang CS, Sim SI, et al. Liver disease during the first post-transplant year in bone marrow transplantation recipients: retrospective study. *Bone Marrow Transplantation* 2000;**26**:193–7.

Kotz 1982 *{published data only}*
Kotz R, Plattner E, Ramach W, Flener R, Bodo G. Interferon/controlled study in 3-year survival of patients with osteosarcoma [Verträglichkeitsprüfung von humanem Lymphoblasten–Interferon. Kontrollierte Studie bei 8 Osteosarkom–Patienten mit 3–Jahres–Überleben]. *Arzneimittel-Forschung* 1982;**32**:446–8.

Kremens 2002 *{published data only}*
Kremens B, Gruhn B, Klingebiel T, Hasan C, Laws HJ, Koscielniak E, et al. High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma. *Bone Marrow Transplantation* 2002;**30**:893–8.

Kudo 1996 *{published data only}*
Kudo T, Morishima T, Tsuzuki K, Orito E, Mizokami M. Hepitits G virus in immunosuppressed paediatric allograft recipients. *Lancet* 1996;**348**:751.

Lackner 2000 *{published data only}*
Lackner H, Benesch M, Schagerl S, Kerbl R, Schwinger W, Urban C. Prospective evaluation of late effects after childhood cancer therapy with a follow-up over 9 years. *European Journal of Pediatrics* 2000;**159**:750–8.

Lackner 2007 *{published data only}*
Lackner H, Moser A, Sovinz P, Benesch M, Schwinger W, Urban C. Long-term care of young adults surviving childhood cancer - where do we go? [Langzeitbetreuung

junger Erwachsener nach Krebserkrankung imKindesalter - Wohin führt der Weg?]. *Wiener Klinische Wochenschrift* 2007;**119**:361–364.

Ladenstein 1997 ***{published data only}***
Ladenstein R, Pearce R, Hartmann O, Patte C, Goldstone T, Philip T. High-dose chemotherapy with autologous bone marrow rescue in children with poor-risk Burkitt's lymphoma: A report from the European lymphoma bone marrow transplantation registry. *Blood* 1997;**90**:2921–30.

Leonardi 2003 ***{published data only}***
Leonardi S, La Spina M, La Rosa M, Schiliro G. Prolylhydroxylase and procollagen type III in long-term survivors of acute lymphoblastic leukemia (ALL): a biochemical approach to HCV-related liver disease. *Medical and Pediatric Oncology* 2003;**41**:17–20.

Leung 2000 ***{published data only}***
Leung W, Hudson MM, Strickland DK, Phipps S, Srivastava DK, Ribeiro RC, et al. Late effects of treatment in survivors of childhood acute myeloid leukemia. *Journal of Clinical Oncology* 2000;**18**:3273–9.

Levitt 2004 ***{published data only}***
Levitt GA, Platt KA, De Byrne R, Sebire N, Owens CM. 4S neuroblastoma: the long-term outcome. *Pediatric Blood and Cancer* 2004;**43**:120–5.

Ljungman 1995 ***{published data only}***
Ljungman P, Johansson N, Aschan J, Glaumann H, Lonnqvist B, Ringden O, et al. Long-term effects of hepatitis C virus infection in allogeneic bone marrow transplant recipients. *Blood* 1995;**86**:1614–8.

Locasciulli 1989 ***{published data only}***
Locasciulli A, Bacigalupo A, Alberti A, van Lint MT, Uderzo C, Marmont AM, et al. Predictability before transplant of hepatic complications following allogeneic bone marrow transplantation. *Transplantation* 1989;**48**:68–72.

Locasciulli 1990a ***{published data only}***
Locasciulli A, Bacigalupo A, van Lint MT, Mura R, Masera G, Tagger G, et al. Hepatitis C virus (HCV) infection in patients with haematological malignancies treated with chemotherapy or bone marrow transplantation (BMT). *Experimental Hematology* 1990;**18**:696.

Locasciulli 1990b ***{published data only}***
Locasciulli A, Uderzo C, Pirola A, Masera G, Portmann B, Alberti A. Pattern of liver disease following high-dose cytosine arabinoside (HDARAC) therapy in children with acute myeloid leukemia. *Leukemia and Lymphoma* 1990;**2**: 229–33.

Locasciulli 1991b ***{published data only}***
Locasciulli A, Bacigalupo A, van Lint MT, Tagger A, Uderzo C, Portmann B, et al. Hepatitis C virus infection in patients undergoing allogeneic bone marrow transplantation. *Transplantation* 1991;**52**:315–8.

Locasciulli 1993 ***{published data only}***
Locasciulli A, Cavalletto D, Pontisso P, Cavalletto L, Scovena E, Uderzo C, et al. Hepatitis C virus serum markers and liver disease in children with leukemia during and after chemotherapy. *Blood* 1993;**82**:2564–7.

Locasciulli 1995 ***{published data only}***
Locasciulli A, Alberti A. Hepatitis C virus serum markers and liver disease in children with leukemia. *Leukemia and Lymphoma* 1995;**17**:245–9.

Maggiore 1982 ***{published data only}***
Maggiore G, Siena S, Prandi M. Hepatitis B and acute lymphoblastic leukemia. *The Journal of Pediatrics* 1982; **101**:156.

Maguire 2002 ***{published data only}***
Maguire AM, Vowels MR, Russell S, Cohn RJ, Cole C, Saxon B, et al. Allogeneic bone marrow transplant improves outcome for juvenile myelomonocytic leukaemia. *Journal of Paediatrics and Child Health* 2002;**38**:166–9.

Martinez 1997 ***{published data only}***
Martinez C, Carreras E, Sierra J, Rovira M, Urbano-Ispizua A, Viguria MC, et al. Second allogeneic progenitor cell transplantation for leukemia relapse: results in 10 patients [Segundo trasplante alogénico de progenitores hematopoyéticos como tratamiento de la recaída leucémica: resultados en 10 pacientes]. *Medicina Clinica* 1997;**109**: 401–5.

Masera 1981 ***{published data only}***
Masera G, Locasciulli A, Jean G, Jankovic M, Rossi MR, Recchia M, et al. Hepatitis B and childhood acute lymphoblastic leukemia. *The Journal of Pediatrics* 1981;**99**: 98–100.

McBride 1976 ***{published data only}***
McBride CM. Primary carcinoma of the liver. *Surgery* 1976; **80**:322–7.

McIntosh 1977 ***{published data only}***
McIntosh S, Davidson DL, O'Brien RT, Pearson HA. Methotrexate hepatotoxicity in children with leukemia. *The Journal of Pediatrics* 1977;**90**:1019–21.

McKay 1996 ***{published data only}***
McKay PJ, Murphy JA, Cameron S, Burnett AK, Campbell M, Tanse P, et al. Iron overload and liver dysfunction after allogeneic or autologous bone marrow transplantation. *Bone Marrow Transplantation* 1996;**17**:63–6.

Meadows 1992 ***{published data only}***
Meadows AT, Gallagher JA, Bunin GR. Late effects of early childhood cancer therapy. *British Journal of Cancer* 1992;**66 Suppl**:92–5.

Mitrou 1990 ***{published data only}***
Mitrou PS, Fischer C, Szepesi S, Heimer K. Results of therapy in Hodgkin's disease [Therapieergebnisse beim Morbus Hodgkin]. *Deutsche Medizinische Wochenschrift* 1990;**115**:1783–9.

Moore 1995 ***{published data only}***
Moore SW, Kaschula ROC, Albertyn R, Rode H, Millar AJW, Karabus C. The outcome of solid tumors occuring in the neonatal period. *Pediatric Surgery International* 1995; **10**:366–70.

Morrow 1982 *{published data only}*
Morrow CE, Grage TB, Sutherland DE, Najarian JS. Hepatic resection for secondary neoplasms. *Surgery* 1982; **92**:610–4.

Murthy 1978 *{published data only}*
Murthy TV, Irving IM, Lister J. Massive adrenal hemorrhage in neonatal neuroblastoma. *Journal of Pediatric Surgery* 1978;**13**:31–4.

Myers 1995 *{published data only}*
Myers B, Irving W, Hollingsworth R, Readett D, Lilleyman JS, Dolan G. Hepatitis C virus infection in multi-transfused children with haematological malignancy. *British Journal of Haematology* 1995;**91**:480–2.

Nagasue 1979 *{published data only}*
Nagasue N, Inokuchi K. Spontaneous and traumatic rupture of hepatoma. *The British Journal of Surgery* 1979; **66**:248–50.

Nagatoshi 1997 *{published data only}*
Nagatoshi Y, Okamura J, Ikuno Y, Akamatsu M, Tasaka H. Therapeutic trial of intensified conditioning regimen with high-dose cytosine arabinoside, cyclophosphamide and either total body irradiation or busulfan followed by allogeneic bone marrow transplantation for myelodysplastic syndrome in children. *International Journal of Hematology* 1997;**65**:269–75.

Neilson 1996 *{published data only}*
Neilson J, Harrison P, Milligan DW, Skidmore SJ, Collingham KE. Hepatitis G virus in long-term survivors of haematological malignancy. *Lancet* 1996;**347**:1632–3.

O'Hara 1968 *{published data only}*
O'Hara JM, Hutter RV, Foote FW Jr, Miller T, Woodard HQ. An analysis of thirty patients surviving longer than ten years after treatment for osteogenic sarcoma. *The Journal of Bone and Joint Surgery. American Volume* 1968;**50**:335–54.

Oeffinger 2006 *{published data only}*
Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *The New England Journal of Medicine* 2006;**355**:1572–82.

Osborne 1980 *{published data only}*
Osborne CK, Norton L, Young RC, Garvin AJ, Simon RM, Berard CW, et al. Nodular histiocytic lymphoma: an aggressive nodular lymphoma with potential for prolonged disease-free survival. *Blood* 1980;**56**:98–103.

Pantoja 1975 *{published data only}*
Pantoja E, Rodriguez-Ibanez I, Axtmayer RW, Noy MA, Pelegrina I. Complications of dermoid tumors of the ovary. *Obstetrics and Gynecology* 1975;**45**:89–94.

Pao 1989 *{published data only}*
Pao WJ, Hustu HO, Douglass EC, Beckford NS, Kun LE. Pediatric nasopharyngeal carcinoma: Long term follow-up of 29 patients. *International Journal of Radiation Oncology, Biology, Physics* 1989;**17**:299–305.

Park 2002 *{published data only}*
Park SH, Lee MH, Lee H, Kim HS, Kim K, Kim WS, et al. A randomized trial of heparin plus ursodiol vs heparin alone to prevent hepatic veno-occlusive disease after hematopoietic stem cell transplantation. *Bone Marrow Transplantation* 2002;**29**:137–43.

Poussin-Rosillo 1976 *{published data only}*
Poussin-Rosillo H, Nisce LZ, D'Angio GJ. Hepatic radiation tolerance in Hodgkins disease patients. *Radiology* 1976;**121**:461–4.

Pratt 1977 *{published data only}*
Pratt C, Shanks E, Hustu O, Rivera G, Smith J, Kumar AP. Adjuvant multiple drug chemotherapy for osteosarcoma of the extremity. *Cancer* 1977;**39**:51–7.

Pritchard 2005 *{published data only}*
Pritchard J, Cotterill SJ, Germond SM, Imeson J, de Kraker J, Jones DR. High dose melphalan in the treatment of advanced neuroblastoma: Results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group. *Pediatric Blood and Cancer* 2005;**44**:348–57.

Pui 1992 *{published data only}*
Pui CH, Simone JV, Hancock ML, Evans WE, Williams DL, Bowman WP, et al. Impact of three methods of treatment intensification on acute lymphoblastic leukemia in children: Long-term results of St Jude total therapy study X. *Leukemia* 1992;**6**:150–7.

Punyko 2005 *{published data only}*
Punyko JA, Mertens AC, Gurney JG, Yasui Y, Donaldson SS, Rodeberg DA. Long-term medical effects of childhood and adolescent rhabdomyosarcoma: A report from the childhood cancer survivor study. *Pediatric Blood and Cancer* 2005;**44**:643–53.

Puri 2006 *{published data only}*
Puri DR, Wexler LH, Meyers PA, La Quaglia MP, Healey JH, Wolden SL. The challenging role of radiation therapy for very young children with rhabdomyosarcoma. *International Journal of Radiation Oncology, Biology, Physics* 2006;**65**:1177–84.

Ravikumara 2006 *{published data only}*
Ravikumara M, Hill FGH, Wilson DC, Gillet PM, Thomas A, Brown R, et al. 6-Thioguanine-related chronic hepatoxicity and variceal haemorrhage in children treated for acute lymphoblastic leukaemia - a dual-centre experience. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**42**: 535–8.

Reaman 1985 *{published data only}*
Reaman G, Zeltzer P, Bleyer WA. Acute lymphoblastic leukemia in infants less than one year of age: A cumulative experience of the Childrens Cancer Study Group. *Journal of Clinical Oncology* 1985;**3**:1513–21.

Rodriguez-Inigo 1997 *{published data only}*
Rodriguez-Inigo E, Tomás JF, Gómez-García de Soria V, Bartolomé J, Pinilla I, Amaro MJ, et al. Hepatitis C and G virus infection and liver dysfunction after allogeneic bone marrow: results from a prospective study. *Blood* 1997;**90**: 1326–31.

Rossetti 1992 *{published data only}*

Rossetti F, Cesaro S, Pizzocchero P, Cadrobbi P, Guido M, Zanesco L. Chronic hepatitis B surface antigen-negative hepatitis after treatment of malignancy. *The Journal of Pediatrics* 1992;**121**:39–43.

Samuelsson 1999 *{published data only}*

Samuelsson BO, Ridell B, Rockert L, Gustafsson G, Marky I. Non-Hodgkin lymphoma in children: a 20-year population-based epidemiologic study in western Sweden. *Journal of Pediatric Hematology/Oncology* 1999;**21**:103–10.

Sawamura 1998 *{published data only}*

Sawamura Y, Ikeda J, Shirato H, Tada M, Abe H. Germ cell tumours of the central nervous system: Treatment consideration based on 111 cases and their long-term clinical outcomes. *European Journal of Cancer* 1998;**34**: 104–10.

Schaison 1980 *{published data only}*

Schaison G, Jacquillat C, Lemercier N, Weil M, Alby N, Auclerc MF, et al. Acute leukemia in childhood: present status of 100 cases after 7 years of complete remission [Leucémië aigu. Bilan de 100 enfents en rémission plus 7 ans]. *Bulletin du Cancer* 1980;**67**:261–8.

Sekine 1998 *{published data only}*

Sekine I, Dobashi H, Kogawa K, Hirota T, Katano N, Kawakami K, et al. Hepatitis C virus infection and chronic liver diseases after treatment of malignant disease in children: A multicenter study from the Children's Cancer and Leukemia Study Group of Japan. *International Journal of Clinical Oncology* 1998;**3**:247–52.

Sevinir 2003 *{published data only}*

Sevinir B, Meral A, Günay Ü, Özkan T, Özuysal S, Sinirtas M. Increased risk of chronic hepatitis in children with cancer. *Medical and Pediatric Oncology* 2003;**40**:104–10.

Shah 2004 *{published data only}*

Shah AJ, Lenarsky C, Kapoor N, Crooks GM, Kohn DB, Parkman R. Busulfan and Cyclophosphamide as a Conditioning Regimen for Pediatric Acute Lymphoblastic Leukemia Patients Undergoing Bone Marrow Transplantation. *Journal of Pediatric Hematology/ Oncology* 2004;**26**:91–7.

Silverman 1997 *{published data only}*

Silverman LB, McLean TW, Gelber RD, Donnelly MJ, Gary GD, Tarbell NJ, et al. Intensified therapy for infants with acute lymphoblastic leukemia: Results from the Dana-Farber Cancer Institute Consortium. *Cancer* 1997;**80**: 2285–95.

Skidmore 1997 *{published data only}*

Skidmore SJ, Collingham KE, Harrison P, Neilson JR, Pillay D, Milligan DW. High prevalence of hepatitis G virus in bone marrow transplant recipients and patients treated for leukemia.. *Blood* 1997;**89**:3853–6.

Socié 1999 *{published data only}*

Socié G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. *The New England Journal of Medicine* 1999;**341**:14–21.

Socié 2001 *{published data only}*

Socié G, Clift RA, Blaise D, Devergie A, Ringden O, Martin PJ, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: Long-term follow-up of 4 randomized studies. *Blood* 2001;**98**: 3569–74.

Spunberg 1981 *{published data only}*

Spunberg JJ, Chang CH, Goldman M. Quality of long-term survival following irradiation for intracranial tumors in children under the age of two. *International Journal of Radiation Oncology, Biology, Physics* 1981;**7**:727–36.

Strasser 1999a *{published data only}*

Strasser SI, Sullivan KM, Myerson D, Spurgeon CL, Storer B, Schoch HG, et al. Cirrhosis of the liver in long-term marrow transplant survivors. *Blood* 1999;**93**:3259–66.

Strasser 1999b *{published data only}*

Strasser SI, Myerson D, Spurgeon CL, Sullivan KM, Storer B, Schoch HG, et al. Hepatitis C virus infection and bone marrow transplantation: A cohort study with 10-year-follow-up. *Hepatology* 1999;**29**:1893–1899.

Straus 1991 *{published data only}*

Straus DJ, Wong G, Yahalom J, Varsos G, Gulati S, Clarkson B. Diffuse large cell lymphoma. Prognostic factors with treatment. *Leukemia* 1991;**5 Suppl 1**:32–7.

Tada 1997 *{published data only}*

Tada K, Tajiri H, Kozaiwa K, Sawada A, Guo W, Okada S. Role of screening for hepatitis C virus in children with malignant disease who undergo bone marrow transplantation. *Transfusion* 1997;**37**:641–4.

Taylor 1997 *{published data only}*

Taylor RE. Morbidity from abdominal radiotherapy in the first United Kingdom Children's Cancer Study Group Wilms' Tumour Study. *Clinical Oncology* 1997;**9**:381–4.

Tefft 1977 *{published data only}*

Tefft M. Radiation related toxicities in National Wilms' Tumor Study Number 1. *International Journal of Radiation Oncology, Biology, Physics* 1977;**2**:455–63.

Thomas 1988 *{published data only}*

Thomas PR, Tefft M, D'Angio GJ, Norkool P. Acute toxicities associated with radiation in the second National Wilms' Tumor Study. *Journal of Clinical Oncology* 1988;**6**: 1694–8.

Tomás 2000 *{published data only}*

Tomás JF, Pinilla I, García-Buey ML, García A, Figuera A, Gómez-García de Soria V, et al. Long-term liver dysfunction after allogeneic bone marrow transplantation: clinical features and course in 61 patients. *Bone Marrow Transplantation* 2000;**26**:649–55.

Tura 1998 *{published data only}*

Tura S, Rosti G, de Vivo A, Bonifazi F, Fiacchini M, Baccarani M, et al. Long-term follow-up of the Italian trial of interferon-alpha versus conventional chemotherapy in chronic myeloid leukemia. *Blood* 1998;**92**:1541–8.

Uchino 1978 *{published data only}*
Uchino J, Hata Y, Kasai Y. Stage IVS neuroblastoma. *Journal of Pediatric Surgery* 1978;**13**:167–72.

Uzel 2001 *{published data only}*
Uzel O, Yoruk SO, Sahinler I, Turkan S, Okkan S. Nasopharyngeal carcinoma in childhood: long-term results of 32 patients. *Radiotherapy and Oncology* 2001;**58**:137–41.

Vaidya 2000 *{published data only}*
Vaidya S, Atra A, Bahl S, Pinkerton CR, Calvagna V, Horton C, et al. Autologous bone marrow transplantation for childhood acute lymphoblastic leukaemia in second remission - Long-term follow-up. *Bone Marrow Transplantation* 2000;**25**:599–603.

van den Ouweland 1983 *{published data only}*
van den Ouweland FA, Holdrinet RSG, de Pauw BE, Haanen O. Transaminase, hepatitis B, and prognosis in acute nonlymphoblastic leukemia. *The New England Journal of Medicine* 1983;**309**:990.

Veneri 2003 *{published data only}*
Veneri D, Franchini M, Zanetti F, Krampera M, de Matteis G, Pizzolo G. Iron overload in acute myeloid leukemia patients is not related to HFE and TFR2 gene mutations. *Haematologica* 2003;**88**:1069–70.

Vergani 1982 *{published data only}*
Vergani D, Locasciulli A, Masera G, Alberti A, Moroni G, Tee DEH, et al. Histologic evidence of hepatitis-B-virus infection with negative serology in children with acute leukemia who develop chronic liver disease. *Lancet* 1982; **13**:361–4.

von Schweinitz 1994 *{published data only}*
von Schweinitz D, Bürger D, Bode U, Weinel P, Erttmann R, Hecker H, et al. Results of the HB-89 Study in treatment of malignant epithelial liver tumors in childhood and concept of a new HB-94 protocol [Ergebnisse der Studie HB–89 bei Behandlung maligner epithelialer Lebertumoren des Kindesalters und Konzept eines neuen Protokolls HB–94]. *Klinische Pädiatrie* 1994;**206**:282–8.

Wasserheit 1995 *{published data only}*
Wasserheit C, Acaba L, Gulati S. Abnormal liver function in patients undergoing autologous bone marrow transplantation for hematological malignancies. *Cancer Investigation* 1995;**13**:347–54.

Weirich 2004 *{published data only}*
Weirich A, Ludwig R, Graf N, Abel U, Leuschner I, Vujanic GM, et al. Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity. *Annals of Oncology* 2004;**15**:808–20.

Wexler 1996 *{published data only}*
Wexler LH, Andrich MP, Venzon D, Berg SL, Weaver-McClure L, Chen CC, et al. Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. *Journal of Clinical Oncology* 1996;**14**:362–72.

Willers 2001 *{published data only}*
Willers E, Webber L, Delport R, Kruger M. Hepatitis B--a major threat to childhood survivors of leukaemia/ lymphoma. *Journal of Tropical Pediatrics* 2001;**47**:220–5.

Wolff 2006 *{published data only}*
Wolff JEA, Wagner S, Reinert C, Gnekow A, Kortmann RD, Kuhl J, et al. Maintenance treatment with interferon-gamma and low-dose cyclophosphamide for pediatric high-grade glioma. *Journal of Neuro-Oncology* 2006;**79**:315–21.

Woolfrey 1998 *{published data only}*
Woolfrey AE, Gooley TA, Sievers EL, Milner LA, Andrews RG, Walters M, et al. Bone marrow transplantation for children less than 2 years of age with acute myelogenous leukemia or myelodysplastic syndrome. *Blood* 1998;**92**: 3546–56.

Yamada-Osaki 1999 *{published data only}*
Yamada-Osaki M, Sumazaki R, Tsuchida M, Koike K, Fukushima T, Matsui A. Persistence and clinical outcome of hepatitis G virus infection in pediatric bone marrow transplant recipients and children treated for hematological malignancy. *Blood* 1999;**93**:721–7.

Yang 2005 *{published data only}*
Yang CP, Hung IJ, Jaing TH, Shih LY, Chang WH. Cancer in infants: A review of 82 cases. *Pediatric Hematology and Oncology* 2005;**22**:463–81.

Yang 2006 *{published data only}*
Yang CP, Hung IJ, Jaing TH, Chang WH. Cancers in the infancy: Percent distribution and incidence rates. *Acta Paediatrica Taiwanica* 2006;**47**:273–7.

Zimmermann 2002 *{published data only}*
Zimmermann SY, Klingebiel T, Koehl U, Soerensen J, Schwabe D. Tecelac as antihymocyte globulin in conditioning for childhood allogeneic stem cell transplantation. *Bone Marrow Transplantation* 2002;**29**: 957–62.

Zittoun 1985 *{published data only}*
Zittoun R, Rio B, Marie JP, Blanc CM. AMSA combined with high dose cytosine-arabinoside in acute leukaemia. *Presse Medicale* 1985;**14**:1417–20.

References to studies awaiting assessment

Kovacs 2007 *{published data only}*
Kovacs G, Sapi C, Csoka M, Erdelyi D, Haltrich I, Muller J. Hepatotoxic late side effects in children with haematological malignancies. *Pediatric Blood and Cancer* 2007;**49**:547–8.

Kristinsson 2002 *{published data only}*
Kristinsson VH, Kristinsson JR, Jonmundsson GK, Jonsson OG, Porsson AV, Haraldsson A. Late and long-term effects of leukemia treatment in childhood [Siokmnar of langvinnar aukaverkanir eftir hvitblaeoismeofero i aesku]. *Laeknabladid* 2002;**88**:13–8.

Thavaraj 2006 *{published data only}*
Thavaraj V, Seth R, Arya LS, Kumar R. Screening for problems of pediatric cancer survivors in our center. *Pediatic Blood and Cancer* 2006;**47**:481.

Additional references

Baldo 2008

Baldo V, Baldovin T, Trivello R, Floreani A. Epidemiology of HCV infection. *Current Pharmaceutical Design* 2008;**14**: 1646–54.

Castellino 2004

Castellino S, Lensing S, Riely C, Rai SN, Davila R, Hayden RT, et al. The epidemiology of chronic hepatitis C infection in survivors of childhood cancer: an update of the St Jude Children's Research Hospital hepatitis C seropositive cohort. *Blood* 2004;**103**:2460–6.

Castellino 2010

Castellino S, Muir A, Shah A, Shope S, McMullen K, Ruble K, et al. Hepato-biliary late effects in survivors of childhood and adolescent cancer: A report from the Children's Oncology Group. *Pediatric Blood and Cancer* 2010;**54**:663–9.

Curry 2006

Curry HL, Parkes SE, Powell JE, Mann JR. Caring for survivors of childhood cancer: the size of the problem. *European Journal of Cancer* 2006;**42**:501–8.

Dawson 2005

Dawson LA, Ten Haken RK. Partial volume tolerance of the liver to radiation. *Seminars in Radiation Oncology* 2005; **15**:279–83.

Field 2008

Field KM, Dow C, Michael M. Part I: Liver function in oncology: biochemistry and beyond. *Lancet* 2008;**9**: 1092–101.

Gatta 2009

Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed between 1995-2002. *European Journal of Cancer* 2009;**45**:992–1005.

Geenen 2007

Geenen MM, Cardous-Ubbink MC, Kremer LCM, van den Bos C, van der Pal HJH, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007;**297**:2705–15.

Grimes 2002

Grimes DA, Schultz KF. Cohort studies: marching towards outcomes. *Lancet* 2002;**359**:341–5.

Higgins 2009

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. Available from www.cochrane–handbook.org.

Hudson 2005

Hudson MM. Late gastrointestinal and hepatic effects. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS editor(s). *Survivors of childhood and adolescent cancer. A multidisciplinary approach*. Second Edition. New York: Springer, 2005:181–202.

Kim 2008

Kim WR, Flamm SL, Di Bisceglie AMD, Bodenheimer HC, Public Policy Committee of the American Association for the Study of Liver Disease. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. *Hepatology* 2008;**47**:1363–70.

King 2001

King PD, Perry MC. Hepatotoxicity of chemotherapy. *The Oncologist* 2001;**6**:162–76.

Kurbegov 2009

Kurbegov AC, Sokol RJ. Hepatitis B therapy in children. *Expert Review of Gasteroenterology & Hepatology* 2009;**3**: 39–49.

Laupacis 1994

Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. *JAMA* 1994;**272**:234–7.

Leung 2007

Leung W, Ahn H, Rose SR, Phipps S, Smith T, Gan K, et al. A prospective cohort study of late sequelae of pediatric allogeneic hematopoietic stem cell transplantation. *Medicine* 2007;**86**:215–24.

Locasciulli 1997

Locasciulli A, Testa M, Valsecchi MG, Vecchi I, Longoni D, Sparano P, et al. Morbidity and mortality due to liver disease in children undergoing allogeneic bone marrow transplantation: a 10-year prospective study. *Blood* 1997; **90**:3799–805.

Rizzo 2006

Rizzo JD, Wingard JR, Tichelli A, Lee SJ, van Lint MT, Burns LJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. *Biology of Blood and Marrow Transplantation* 2006;**12**:138–51.

Ruhl 2009

Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. *Gastroenterology* 2009;**136**:477–85.

Saleh 2007

Saleh HA, Abu-Rashed AH. Liver biopsy remains the gold standard for evaluation of chronic hepatitis and fibrosis. *Journal of Gastrointestinal and Liver Diseases* 2007;**16**:425–6.

Strasser 1999

Strasser SI, Sullivan KM, Myerson D, Spurgeon CL, Storer B, Schoch HG, et al. Cirrhosis of the liver in long-term marrow transplant survivors. *Blood* 1999;**93**:3259–66.

Strickland 2000

Strickland DK, Riely CA, Patrick CC, Jones-Wallace D, Boyett JM, Waters B, et al. Hepatitis C infection among survivors of childhood cancer. *Blood* 2000;**95**:3065–70.

Villano 1999

Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology* 1999;**29**:908–14.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aricò 1994

Methods	Cohort study
Participants	*N* of patients original cohort: 102; *N* of patients described study group: 102; *N* of patients study group of interest: 102; *N* of patients with liver function tests: 102 Tumour: ALL; Time period diagnosis/treatment: 1977-1992; Age at diagnosis: nm; Age at follow-up: median 10.5 (2.5-21.1) yr; F/M%: 45/55; BMI: nm *N* of patients hepatitis virus infection: 23/102 (22.5%) anti-HCV$^+$, HCV-RNA$^+$ and 7/102 (6.8%) anti-HCV$^+$, HCV-RNA$^-$ *N* of patients acute liver disease: nm Follow-up duration: median 2.8 (0.1-12.5) yr after end of treatment; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 102/102 (100%); Chemotherapy type: nm; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: 101/102 (99.0%)
Outcomes	Method of detection of hepatic late adverse effects: ALT (frequency of testing nm) Definition of hepatic late adverse effects: ALT > upper limit of normal (35 IU/mL) *N* of patients hepatic late adverse effects at end of follow-up: 22/102 (21.6%) of whom 5/102 (4.9%) had mild-to-moderate increase, 16/102 (15.7%) moderate increase and 1/102 (1.0%) severe increase (>3.5 times upper limit of normal (35 IU/mL)) Risk factors: Chronic HCV infection: 16/23 (69.6%) with chronic HCV infection elevated ALT versus 6/79 (7.6%) without chronic HCV infection elevated ALT (P<0.001) (Univariate)
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account

Aricò 1994 (*Continued*)

Well defined study group	High risk	Type of chemotherapy was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Ballauff 1999

Methods	Prospective cohort study
Participants	*N* of patients original cohort: 50; *N* of patients described study group: 50; *N* of patients study group of interest: 50; *N* of patients with liver function tests: 50 Tumour: various tumours; Time period diagnosis/treatment: 1980-1991; Age at diagnosis: nm; Age at follow-up: median 12.3 (6.7-24.5) yr; F/M%: 36/64; BMI: nm *N* of patients hepatitis virus infection: 14/50 (28.0%) anti-HCV$^+$, HCV-RNA$^+$, 2/50 (4.0%) anti-HCV$^+$, HCV-RNA$^-$ and 2/50 (4.0%) HBsAntigen$^+$ *N* of patients acute liver disease: 43/50 (86.0%) elevated AST/ALT during chemotherapy; 13/50 (26.0%) elevated bilirubin and GGT during chemotherapy Follow-up duration: median 3.6 (0.5-11.8) yr after end of treatment; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 50/50 (100%); Chemotherapy type: nm; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: 50/50 (100%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, bilirubin, GGT (frequency of testing nm) Definition of hepatic late adverse effects: ALT > normal (24 U/L), AST > normal (22 U/L), bilirubin >1.5 mg/dL (normal: 0.3 mg/dL), GGT >100 U/L (normal: 20 U/L) *N* of patients hepatic late adverse effects at end of follow-up: 16/50 (32.0%) Risk factors: Chronic HBV/HCV infection: 13/16 (81.3%) with abnormal liver function tests chronic HBV/HCV infection versus 2/34 (5.9%) with normal liver function tests chronic HBV/HCV infection (P=0.001) (Univariate)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort

Ballauff 1999 (*Continued*)

Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Bessho 1994

Methods	Cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 25; *N* of patients study group of interest: 25; *N* of patients with liver function tests: 25 Tumour: ALL; Time period diagnosis/treatment: nm; Age at diagnosis: median 4.4 (1.2-15.0) yr; Age at follow-up: median 15.0 (6.8-22.0) yr; F/M%: 41/59; BMI: nm *N* of patients hepatitis virus infection: 0/23 (0.0%) anti-HCV^+ and 0/23 (0.0%) $HBsAntigen^+$ *N* of patients acute liver disease: 24/25 (96.0%) elevated ALT during chemotherapy and 20/25 (80.0%) elevated ALT at end chemotherapy Follow-up duration: median 4.2 (1.0-7.5) yr after end of treatment; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 25/25 (100%); Chemotherapy type: prednisolone, vincristine, daunorubicin, L-asparaginase, methotrexate and 6-mercaptopurine; Chemotherapy dose: Induction therapy consisted of daily prednisolone 60 mg/m^2 for 4 weeks, 5 doses of weekly vincristine 1.5 mg/m^2, 5 doses of weekly daunorubicin 25 mg/m^2 and 4 doses of weekly L-asparaginase 10,000 U/m^2 or 8 doses of biweekly L-asparaginase 6000 U/m^2. Prophylaxis of central nervous system leukaemia consisted of 5 doses weekly methotrexate 12 mg/m^2. Maintenance therapy consisted of daily 6-mercaptopurine and weekly methotrexate. Initial doses of methotrexate and 6-mercaptopurine were 20 mg/m^2 and 50 mg/m^2, respectively. Mean methotrexate dose actually administered: 3.35 ± 1.27 g/m^2. Mean 6-mercaptopurine dose actually administered: 59.65 ± 21.16 g/m^2 *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: 23/25 (92.0%)

Bessho 1994 (*Continued*)

Outcomes	Method of detection of hepatic late adverse effects: ALT, bilirubin, albumin, PTT (measured 3-12 monthly 1 yr after the end of treatment) Definition of hepatic late adverse effects: ALT > upper limit of normal (33.3 IU/L); bilirubin, albumin, PTT: nm *N* of patients hepatic late adverse effects at end of follow-up: ALT: 2/25 (8.0%); bilirubin, albumin and PTT: 0/25 (0.0%) Risk factors: not evaluated
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	Low risk	Type of chemotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Bresters 2008

Methods	Retrospective cohort study
Participants	*N* of patients original cohort: 290; *N* of patients described study group: 216; *N* of patients study group of interest: 216; *N* of patients with liver function tests: 216 Tumour: ALL, AML, CML, JMML, MDS, lymphoma (n=129), benign haematological disease (n=54), immunological disease (n=22), other inborn errors (n=11); Time period diagnosis/ treatment: 1980-2002; Age at diagnosis: nm (age at HSCT: median 7.6 (0.1-18.4) yr); Age at follow-up: nm; F/M%: 40/60; BMI: nm *N* of patients hepatitis virus infection: 3/139 (2.1%) anti-HCV$^+$ and 0/183 (0.0%) HBsAntigen$^+$ *N* of patients acute liver disease: 14/216 (6.5%) VOD and 5/216 (2.3%) acute GVHD Follow-up duration: 2 yr after HSCT, plus or minus 6 months; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 211/216 (97.7%); Chemotherapy type: cyclophosphamide (n=121), cyclophosphamide with busulphan (n=69), other unspecified (n=21); Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: 132/216 (61.1%); Radiotherapy field: TBI/

	TAI; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: 216/216 (100%) *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST (frequency of testing nm) Definition of hepatic late adverse effects: ALT and/or AST > upper limit of normal (mean plus 2 standard deviations as determined in a normal Dutch population) *N* of patients hepatic late adverse effects at end of follow-up: 53/216 (24.5%) of whom 17/216 (7.9%) had ALT/AST ≥2 times upper limit of normal. In 12/13 (92.3%) patients with ALT/AST ≥2 times upper limit of normal persisting abnormal liver enzymes 3 years after HSCT Risk factors: Older age at HSCT: median age 9.9 yr in patients with elevated ALT/AST versus 7.2 yr in patients with normal ALT/AST (P=0.027); diagnosis of benign haematological disease (OR, 2.59; 95% CI, 1.32-5.05) (P=0.005); gender, donor type (matched sibling donor, other), stem cell source (bone marrow, autologous peripheral blood, cord blood), conditioning regimen (cyclophosphamide with TBI/TAI, cyclophosphamide with busulphan, other) and early post-transplant morbidity (viral reactivation after HSCT, VOD, acute GVHD) (ns) (Univariate)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy, location of radiotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Odds ratio, mean difference and Chi^2 were calculated

Chotsampancharoen 2009

Methods	Prospective cohort study
Participants	*N* of patients original cohort: 205[a]; *N* of patients described study group: 133; *N* of patients study group of interest: 133; *N* of patients with liver function tests: nm Tumour: ALL, AML, CML; Time period diagnosis/treatment: 1990-2005; Age at diagnosis: nm (age at HSCT: mean 9.1 ± 5.6 (0.6-21.4) yr); Age at follow-up: nm; F/M%: 46/54; BMI: nm *N* of patients hepatitis virus infection: nm *N* of patients acute liver disease: nm Follow-up duration: mean 5.6 ± 3.5 (1-15) yr after HSCT; Completion of follow-up: unclear
Interventions	*N* of patients chemotherapy: nm; Chemotherapy type: nm; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: 127/133 (95.5%); Radiotherapy field: TBI; Radiotherapy dose: 8-14.4 Gy[a] *N* of patients hepatectomy: nm *N* of patients BMT: 133/133 (100%) *N* of patients blood transfusion: 133/133 (100%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, total bilirubin (frequency of testing nm) Definition of hepatic late adverse effects: nm *N* of patients hepatic late adverse effects at end of follow-up: nm Risk factors: High serum ferritin (iron overload): serum ferritin was positively correlated with ALT (r=0.17) and total bilirubin (r=0.21) (P<0.001) (Univariate)
Notes	[a] Reported in Leung 2007

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Unclear risk	Unclear if outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Number of patients with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned

Chotsampancharoen 2009 (*Continued*)

Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Frisk 1998

Methods	Retrospective and prospective cohort study
Participants	*N* of patients original cohort: 40; *N* of patients described study group: 40; *N* of patients study group of interest: 40; *N* of patients with liver function tests: 40 Tumour: ALL, AML, NHL, HL (n=30), non-malignant disease (n=10); Time period diagnosis/ treatment: From 1985 onwards; Age at diagnosis: nm (age at BMT: median 7.6 (0.5-18.2) yr[a]; Age at follow-up: nm; F/M%: 39/61[a]; BMI: nm *N* of patients hepatitis virus infection: 1/40 (2.5%) anti-HCV^+, $HCV\text{-}RNA^+$ *N* of patients acute liver disease: 52/64 (81.3%) elevated aminotransferases and/or bilirubin early after BMT[a]; 3/64 (4.7%) VOD[a]; 4/64 (6.3%) acute GVHD[a] Follow-up duration: median 5.0 (1.0-10.0) yr after BMT; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: minimal 33/40 (82.5%); Chemotherapy type: prednisone, teniposide, daunorubicin, vincristine, cyclophosphamide, busulphan, BCNU, etoposide, cytarabine, cyclosporin and methotrexate; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: 20/40 (50.0%); Radiotherapy field: TBI; Radiotherapy dose: 7.5 Gy *N* of patients hepatectomy: nm *N* of patients BMT: 40/40 (100%) *N* of patients blood transfusion: minimal 1/40 (2.5%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, ALP, bilirubin, PTT (measured annually 1 yr after BMT) Definition of hepatic late adverse effects: nm *N* of patients hepatic late adverse effects at end of follow-up: 6/40 (15.0%) Risk factors: not evaluated
Notes	[a] Data of 64 patients with BMT

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant

Frisk 1998 (*Continued*)

Well defined study group	Low risk	Type of chemotherapy, location of radiotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Guido 1991

Methods	Cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 54 with liver biopsy within 3 months after end chemotherapy; *N* of patients study group of interest: 54; *N* of patients with liver function tests: 19 with abnormal liver function 3 months after chemotherapy Tumour: ALL; Time period diagnosis/treatment: 1979-1988; Age at diagnosis: mean 5.0, median 4.5 (1.5-11.0) yr[a]; Age at follow-up: nm; F/M%: 49/51[a]; BMI: nm *N* of patients hepatitis virus infection: 6/19 (31.6%) anti-HCV$^+$, 4/19 (21.1%) HBsAntigen$^+$ of whom 1/19 (5.3%) anti-HDV$^+$ co-infection *N* of patients acute liver disease: 19/19 (100%) elevated ALT during chemotherapy; liver biopsy 3 months after end chemotherapy: 7/19 (36.8%) fibrosis, 8/19 (42.1%) acute hepatitis, 2/19 (10.5%) chronic persistent hepatitis, 1/19 (5.3%) chronic lobular hepatitis, 1/19 (5.3%) chronic active hepatitis and 0/19 (0.0%) cirrhosis Follow-up duration: mean 3.2 (2-7) yr after end of treatment[a]; Completion of follow-up: 35.2%
Interventions	*N* of patients chemotherapy: 19/19 (100%); Chemotherapy type: vincristine, prednisone, L-asparaginase, doxorubicin, daunorubicin, methotrexate, 6-mercaptopurine, cytosine arabinoside, 6-thioguanine, cyclophosphamide, hydroxyurea, BCNU; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: 19/19 (100%)
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 3-6 monthly 1 yr after the end of treatment) Definition of hepatic late adverse effects: elevated ALT *N* of patients hepatic late adverse effects at end of follow-up: 16/19 (84.2%) Risk factors: not evaluated
Notes	[a] Data of 72 patients with ALL with liver biopsy within 3 months after chemotherapy

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Guido 1991 (*Continued*)

Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	High risk	Outcome was assessed for less than 60% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	Low risk	Type of chemotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Jagt 2009

Methods	Retrospective cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 91; *N* of patients study group of interest: 91; *N* of patients with liver function tests: 64 Tumour: Wilms' tumour; Time period diagnosis/treatment: 1986-2006; Age at diagnosis: range 0.2-10.9 yr[a]; Age at follow-up: nm; F/M%: 40/60[a]; BMI: nm *N* of patients hepatitis virus infection: nm *N* of patients acute liver disease: minimal 13/64 (20.3%) VOD Follow-up duration: nm (≥5 yr after end of treatment); Completion of follow-up: 70.3%
Interventions	*N* of patients chemotherapy: 64/64 (100%); Chemotherapy type: vincristine, actinomycin, epirubicin and doxorubicin; Chemotherapy dose: weekly 1.5 mg/kg vincristine, 4 courses 15 μg/kg actinomycin on 3 subsequent days, or 2 courses 15 μg/kg actinomycin on 3 subsequent days, or 2 courses 45 μg/kg actinomycin once every 2 weeks, and 2 courses 50 mg/m^2 epirubicin or doxorubicin *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, GGT, ALP (frequency of testing nm) Definition of hepatic late adverse effects: any value higher than age-dependent upper limit of normal *N* of patients hepatic late adverse effects at end of follow-up: 33/64 (51.6%) Risk factors: not evaluated
Notes	[a] Data of 91 patients in the described study group

Risk of bias ***Risk of bias***

Jagt 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	High risk	Number of patients with hepatitis virus infection was not mentioned
Well defined follow-up	High risk	Length of follow-up was not mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Locasciulli 1983

Methods	Retrospective and prospective cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 70 with abnormal liver function during chemotherapy; *N* of patients study group of interest: 70; *N* of patients with liver function tests: 56 Tumour: ALL, ANLL; Time period diagnosis/treatment: 1972-1981; Age at diagnosis: mean 8 (4-19) yr[a]; Age at follow-up: nm; F/M%: 43/57[b]; BMI: nm *N* of patients hepatitis virus infection: 30/56 (53.6%) HBV markers (i.e. antigens or antibodies for HBV) *N* of patients acute liver disease: 56/56 (100%) elevated ALT/AST during chemotherapy; liver biopsy in 38 patients at end chemotherapy: 5/38 (13.1%) chronic lobular hepatitis, 17/38 (44.7%) chronic persistent hepatitis and 9/38 (23.6%) chronic active hepatitis Follow-up duration: mean 2.0 (0.5-7.0) yr after end of treatment; Completion of follow-up: 80.0%
Interventions	*N* of patients chemotherapy: 56/56 (100%); Chemotherapy type: vincristine, prednisone, 6-mercaptopurine, methotrexate, vinblastine, L-asparaginase, daunorubicin, cytosine arabinoside, doxorubicin, cyclophosphamide, 6-thioguanine; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: 53/56 (94.6%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST (measured 3-6 monthly) Definition of hepatic late adverse effects: ALT/AST >3 times upper limit of normal (60 IU/L) for ≥6 months *N* of patients hepatic late adverse effects at end of follow-up: ≥6 months: 22/56 (39.3%), <6

Locasciulli 1983 (*Continued*)

	months: 10/56 (17.9%) Risk factors: Cleared or persistent chronic HBV infection: 17/22 (77.3%) with persistently high transaminases HBV markers versus 3/24 (12.5%) with normal transaminases HBV markers (P<0.001); histological diagnosis of chronic hepatitis: 19/27 (70.4%) with histological diagnosis of chronic hepatitis persistently elevated transaminases versus 1/4 (25.0%) with minimal changes persistently elevated transaminases (P<0.005) (Univariate)
Notes	[a] Data of 103 patients with ALL/ANLL [b] Data of 70 patients in the original cohort

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Locasciulli 1985

Methods	Prospective cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 89 with abnormal liver function during chemotherapy; *N* of patients study group of interest: 89; *N* of patients with liver function tests: 48 Tumour: ALL, ANLL; Time period diagnosis/treatment: 1979; Age at diagnosis: mean 4.8 (0.3-14.0) yr[a]; Age at follow-up: nm; F/M%: 46/54[a]; BMI: nm *N* of patients hepatitis virus infection: 23/48 (47.9%) $HBsAntigen^+$ *N* of patients acute liver disease: 48/48 (100%) elevated ALT during chemotherapy

Locasciulli 1985 (*Continued*)

	Follow-up duration: mean 2.8 (0.5-4.1) yr after end of treatment; Completion of follow-up: 53.9%
Interventions	*N* of patients chemotherapy: 48/48 (100%); Chemotherapy type: vincristine, prednisone, 6-mercaptopurine, methotrexate, L-asparaginase, cytosine arabinoside, 6-thioguanine, doxorubicin, cyclophosphamide, BCNU, daunorubicin; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (frequency of testing nm) Definition of hepatic late adverse effects: ALT >3 times upper limit of normal (60 IU/L) for ≥6 months *N* of patients hepatic late adverse effects at end of follow-up: 33/48 (68.8%) Risk factors: not evaluated
Notes	[a] Data of 164 patients with ALL/ANLL

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	High risk	Outcome was assessed for less than 60% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	Low risk	Type of chemotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Locasciulli 1991a

Methods	Cohort study
Participants	*N* of patients original cohort: 174; *N* of patients described study group: 50 with abnormal liver function during chemotherapy; *N* of patients study group of interest: 50; *N* of patients with liver function tests: 50 Tumour: ALL (n=40), AML (n=8), CML (n=1), RAEB (n=1); Time period diagnosis/treat-

Locasciulli 1991a (*Continued*)

	ment: 1969-1989; Age at diagnosis: mean 5.8 (0.8-16.6) yr; Age at follow-up: nm; F/M%: 40/60; BMI: nm *N* of patients hepatitis virus infection: 12/50 (24.0%) anti-HCV$^+$, RIBA$^+$ and 14/50 (28.0%) HBsAntigen$^+$ *N* of patients acute liver disease: 50/50 (100%) elevated ALT during chemotherapy; liver biopsy in 37 patients at end chemotherapy: 7/37 (18.9%) nonspecific reactive hepatitis, 13/37 (35.1%) chronic lobular hepatitis, 12/37 (32.4%) chronic persistent hepatitis and 10/37 (27.0%) chronic active hepatitis Follow-up duration: mean 6.2 ± 3.4 (1.0-12.6) yr after end of treatment; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 50/50 (100%); Chemotherapy type: nm; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: 13/50 (26.0%) *N* of patients blood transfusion: 48/50 (96.0%)
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 3-6 monthly) Definition of hepatic late adverse effects: ALT > upper limit of normal (40 IU/L) *N* of patients hepatic late adverse effects at end of follow-up: 20/50 (40.0%) Risk factors: Chronic HCV infection: 11/12 (91.7%) with chronic HCV infection persistently elevated ALT versus 8/27 (29.6%) without chronic HCV infection persistently elevated ALT (P=0.0012) (Univariate)
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Locasciulli 1991a (*Continued*)

Well defined risk estimation	Low risk	Mean difference was calculated

Locasciulli 1997a

Methods	Prospective cohort study
Participants	*N* of patients original cohort: 125; *N* of patients described study group: 114; *N* of patients study group of interest: 114; *N* of patients with liver function tests: 114 Tumour: ALL, AML; Time period diagnosis/treatment: 1968-1982; Age at diagnosis: mean 4 ± 2.6 yr; Age at follow-up: nm; F/M%: 48/52; BMI: nm *N* of patients hepatitis virus infection: 28/114 (24.6%) anti-HCV$^+$, HCV-RNA$^+$ and 19/114 (16.7%) anti-HCV$^+$, HCV-RNA$^-$ *N* of patients acute liver disease: 54/111 (48.7%) elevated ALT at end chemotherapy; liver biopsy in 36 patients at end chemotherapy: 5/36 (13.9%) nonspecific reactive hepatitis, 9/36 (25.0%) chronic lobular hepatitis, 15/36 (41.7%) chronic persistent hepatitis and 7/36 (19.4%) chronic active hepatitis Follow-up duration: mean 17 ± 3.2 (13-27) yr after end of treatment; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 114/114 (100%); Chemotherapy type: nm; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured yearly), liver biopsy (n=2 at follow-up of 5 and 7 yr, respectively) Definition of hepatic late adverse effects: ALT > upper limit of normal (42 IU/L) *N* of patients hepatic late adverse effects at end of follow-up: ALT: 33/114 (28.9%) of whom 4/114 (3.5%) had constantly abnormal values and 29/114 (25.4%) fluctuations from normal to abnormal values; liver biopsy: 1/2 (50.0%) chronic persistent hepatitis, 1/2 (50.0%) chronic lobular hepatitis Risk factors: Chronic HCV infection: 22/28 (78.6%) with chronic HCV infection elevated ALT versus 11/86 (12.8%) without chronic HCV infection elevated ALT (P=0.008) (Univariate)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort

Locasciulli 1997a (*Continued*)

Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Locasciulli 1997b

Methods	Prospective cohort study
Participants	*N* of patients original cohort: 53; *N* of patients described study group: 53; *N* of patients study group of interest: 53; *N* of patients with liver function tests: 53 Tumour: ALL, AML, CML, JCML, Histiocytosis X, SAA, RAEB; Time period diagnosis/treatment: 1985-1995; Age at diagnosis: nm (age at BMT: mean 9.4 (0.9-18.0) yr[a]; Age at follow-up: nm; F/M%: 34/66[a]; BMI: nm *N* of patients hepatitis virus infection: minimal 9/53 (17.0%) ant-HCV^+, $HCV\text{-}RNA^+$, minimal 5/53 (9.4%) anti-HCV^+, $HCV\text{-}RNA^-$ and 2/53 (3.8%) $HBsAntigen^+$ *N* of patients acute liver disease: 82/111 (73.9%) elevated ALT after BMT[a]; 4/111 (3.6%) VOD leading to multi-organ failure[a] Follow-up duration: range 1.3-10.9 yr after BMT; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 53/53 (100%); Chemotherapy type: cyclophosphamide, cytarabine, vincristine, etoposide, busulphan, melphalan, cyclosporine and methotrexate; Chemotherapy dose: 120 mg/kg cyclophosphamide was given as 2 daily doses of 60 mg/kg, alone, or in combination with high-dose cytarabine 3 mg/m^2 for 2 days, high-dose vincristine 4 mg/m^2 in 4 days, etoposide 60mg/kg in 1 day, busulphan 16 mg/kg as 4 daily doses and melphalan 140 mg/m^2. Children with SAA were conditioned with 200 mg/kg cyclophosphamide given in divided doses on 4 days. Cyclosporine and methotrexate dose: nm *N* of patients radiotherapy involving the liver: nm (76/111 (68.5%))[a]; Radiotherapy field: TBI; Radiotherapy dose: 12 Gy *N* of patients hepatectomy: nm *N* of patients BMT: 53/53 (100%) *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 3 monthly) Definition of hepatic late adverse effects: ALT > upper limit of normal (42 IU/L) for ≥6 months *N* of patients hepatic late adverse effects at end of follow-up: 28/53 (52.8%)

Locasciulli 1997b (*Continued*)

	Risk factors: not evaluated
Notes	[a] Data of 111 patients with BMT

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	Low risk	Type of chemotherapy, location of radiotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Matsuzaki 2001

Methods	Prospective cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 132; *N* of patients study group of interest: 132; *N* of patients with liver function tests: 105 Tumour: ALL; Time period diagnosis/treatment: 1984-1990; Age at diagnosis: nm; Age at follow-up: nm; F/M%: 42/58[a]; BMI: nm (one patient with obesity) *N* of patients hepatitis virus infection: 9/105 (8.6%) HCV infection (not specified) *N* of patients acute liver disease: nm Follow-up duration: nm; Completion of follow-up: 79.5%
Interventions	*N* of patients chemotherapy: 105/105 (100%); Chemotherapy type: vincristine, prednisolone, L-asparaginase, daunorubicin, cytosine arabinoside, methotrexate, 6-mercaptopurine, enocitabine, doxorubicin, dexamethasone and cyclophosphamide[a]; Chemotherapy dose: induction consisted of 4 times 2 mg/m^2 vincristine, 4 weeks 60 mg/m^2 prednisolone, 7 times 10,000 U/m^2 L-asparaginase, 2 times 25 mg/m^2 daunorubicin and 4 times 500 mg/m^2 cytosine arabinoside. Consolidation consisted of 300 + 400 mg/m^2 or 2 times 500 mg/m^2 methotrexate, 14 days 120 mg/m^2 6-mercaptopurine and 8 times 150 mg/m^2 enocitabine. Reinduction consisted of 4 times 2 mg/m^2 vincristine, 2 to 4 weeks 8 mg/m^2 dexamethasone, 4 times 1 g/m^2 high-dose cytosine arabinoside and 1 time 10,000 U/m^2 L-asparaginase. Maintenance consisted of 4 days 120 mg/m^2 6-mercaptopurine, 600 mg/m^2 intravenous cyclophosphamide, 4 days 70 mg/m^2 cyclophosphamide by mouth, 45 mg/m^2 daunorubicin, 200 mg/m^2 cytosine arabinoside, 4 days 10 mg/m^2 methotrexate and 2 mg/m^2 vincristine[a] *N* of patients radiotherapy involving the liver: 0 (0.0%); Radiotherapy field: not applicable; Ra-

Matsuzaki 2001 (*Continued*)

	diotherapy dose: not applicable *N* of patients hepatectomy: nm *N* of patients BMT: 0 (0.0%) *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: transaminase (frequency of testing nm) Definition of hepatic late adverse effects: transaminase <100 IU/L *N* of patients hepatic late adverse effects at end of follow-up: 19/105 (18.1%) Risk factors: not evaluated
Notes	[a] Data of 187 patients with ALL

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	Low risk	Type of chemotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	High risk	Length of follow-up was not mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Ratner 1986

Methods	Retrospective cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 39; *N* of patients study group of interest: 39; *N* of patients with liver function tests: 39 Tumour: ALL; Time period diagnosis/treatment: 1971-1980; Age at diagnosis: nm; Age at follow-up: nm; F/M%: nm; BMI: nm *N* of patients hepatitis virus infection: 5/39 (12.8%) $HBsAntigen^+$ of whom 3/39 (7.7%) $anti\text{-}HDV^+$ co-infection *N* of patients acute liver disease: 50/79 (63.3%) elevated ALT during maintenance therapy[a] Follow-up duration: range 1.0-8.3 yr after end of treatment; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 39/39 (100%); Chemotherapy type: vincristine, 6-mercaptopurine, methotrexate, asparaginase, cyclophosphamide, daunorubicin, hydroxyurea and prednisone; Chemotherapy dose: nm

Ratner 1986 (*Continued*)

	N of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 6 monthly), liver biopsy (n=3) Definition of hepatic late adverse effects: ALT >2 times upper limit of normal (90 U/L) *N* of patients hepatic late adverse effects at end of follow-up: ALT: 9/39 (23.1%); liver biopsy: 3/3 (100%) cirrhosis Risk factors: not evaluated
Notes	[a] Data of 79 patients with ALL

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	Low risk	Type of chemotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Rossetti 1991

Methods	Cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 145; *N* of patients study group of interest: 145; *N* of patients with liver function tests: 96 Tumour: ALL; Time period diagnosis/treatment: 1967-1983; Age at diagnosis: nm; Age at follow-up: range 6-26 yr; F/M%: 49/51; BMI: nm *N* of patients hepatitis virus infection: 60/96 (62.5%) $HBsAntigen^+$ of whom 30/96 (31.3%) $anti\text{-}HDV^+$ co-infection *N* of patients acute liver disease: 40/96 (41.7%) elevated ALT during chemotherapy; liver biopsy in 72 patients within 3 months after chemotherapy: 27/72 (37.5%) chronic active hepatitis or cirrhosis and 10/72 (13.9%) chronic persistent/lobular hepatitis Follow-up duration: range 4-20 yr from diagnosis, ≥2.0 yr after end of treatment; Completion

Rossetti 1991 (*Continued*)

	of follow-up: 66.2%
Interventions	*N* of patients chemotherapy: 96/96 (100%); Chemotherapy type: vincristine, L-asparaginase, doxorubicin, daunorubicin, methotrexate (high-dose) 6-mercaptopurine, cytosine arabinoside, 6-thioguanine, cyclophosphamide, hydroxyurea and BCNU; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 3 monthly), albumin (frequency of testing nm) Definition of hepatic late adverse effects: ALT >2 times upper limit of normal (100 IU/L); Albumin nm *N* of patients hepatic late adverse effects at end of follow-up: ALT:43/96 (44.8%); Albumin: 0/96 (0.0%) Risk factors: Chronic HBV-HDV co-infection and chronic HBV infection: 27/30 (90.0%) with chronic HBV-HDV co-infection elevated ALT versus 10/26 (38.5%) with chronic HBV infection elevated ALT versus 6/40 (15.0%) without chronic HBV infection elevated ALT (P<0.02) (Univariate)
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy and number of patients with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Stringer 1995

Methods	Retrospective cohort study
Participants	*N* of patients original cohort: 26; *N* of patients described study group: 26; *N* of patients study group of interest: 26; *N* of patients with liver function tests: 26 Tumour: Hepatoblastoma; Time period diagnosis/treatment: 1981-1993; Age at diagnosis: median 1.3 (0.0 - 12.0)[a]; Age at follow-up: nm; F/M%: 39/61[a]; BMI: nm *N* of patients hepatitis virus infection: nm *N* of patients acute liver disease: nm Follow-up duration: median 5.3 (0.1-12.2) yr; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 24/26 (92.3%); Chemotherapy type: cisplatin, doxorubicin, carboplatin and etoposide; Chemotherapy dose: 3-weekly cisplatin (80-100 mg/m^2) and doxorubicin (50-60 mg/m^2) *N* of patients radiotherapy involving the liver: 2/26 (7.7%); Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: 26/26 (100%) *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: Biochemical liver function tests (frequency of testing nm) Definition of hepatic late adverse effects: nm *N* of patients hepatic late adverse effects at end of follow-up: 0/26 (0.0%) Risk factors: not evaluated
Notes	[a] Data of 41 patients with hepatoblastoma

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	High risk	Number of patients with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Tefft 1970

Methods	Retrospective cohort study
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 99; *N* of patients study group of interest: 99; *N* of patients with liver function tests: 88 Tumour: Wilms' tumour, neuroblastoma, hepatoma; Time period diagnosis/treatment: nm; Age at diagnosis: 14% <1 yr, 56% 1-4 yr, 30% >5 yr[a]; Age at follow-up: nm; F/M%: 55/45[a]; BMI: nm *N* of patients hepatitis virus infection: nm *N* of patients acute liver disease: 31/51 (60.8%) abnormal liver function within 6 months following radiotherapy Follow-up duration: mean 3.9 (0.5-13.3) yr after end of treatment; Completion of follow-up: 88.9%
Interventions	*N* of patients chemotherapy: 88/88 (100%); Chemotherapy type: vincristine, actinomycin D and 5-fluorouracil; Chemotherapy dose: nm *N* of patients radiotherapy involving the liver: 88/88 (100%); Radiotherapy field: right lobe (n=36), left lobe (n=35), entire liver (n=13), remaining liver after resection (n=4); Radiotherapy dose: <25 Gy (n=21), 25-35 Gy (n=47), >35 Gy (n=20) *N* of patients hepatectomy: 4/88 (4.5%) *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: AST and other unspecified liver function tests (frequency of testing nm) Definition of hepatic late adverse effects: Abnormal liver function tests *N* of patients hepatic late adverse effects at end of follow-up: 51/88 (58.0%) Risk factors: site of radiotherapy: 25/36 (96.4%) with right lobe irradiation abnormal liver function tests versus 16/35 (45.7%) with left lobe irradiation abnormal liver function tests versus 6/13 (46.2%) with whole liver irradiation abnormal liver function tests versus 4/4 (100%) with remaining liver irradiation abnormal liver function tests (ns); radiotherapy dose: 11/21 (52.4%) with <25 Gy abnormal liver function tests versus 27/47 (57.4%) with 25-35 Gy abnormal liver function tests versus 12/20 (60.0%) with >35 Gy abnormal liver function tests (ns) (Univariate)
Notes	[a] Data of 115 patients

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant

Tefft 1970 (*Continued*)

Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Number of patients with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Vora 2006

Methods	Prospective cohort study (originally developed as a RCT; a selected group of patients was followed up for hepatic late adverse effects)
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 43 with splenomegaly during chemotherapy; *N* of patients study group of interest: 43; *N* of patients with liver function tests: 43 Tumour: lymphoblastic leukaemia; Time period diagnosis/treatment: 1997-2002; Age at diagnosis: 1.0-18.0 yr; Age at follow-up: nm; F/M%: nm; BMI: nm *N* of patients hepatitis virus infection: nm *N* of patients acute liver disease: 0/43 (0.0%) abnormal liver function tests <1 yr after end chemotherapy Follow-up duration: mean 3.3 (0.0-5.4) yr after end of treatment; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 43/43 (100%); Chemotherapy type: 6-thioguanine, 6-mercaptopurine, vincristine, methotrexate, L-asparaginase, prednisolone, dexamethasone (other chemotherapeutic regimens not mentioned); Chemotherapy dose: 40 mg/m^2/day 6-thioguanine, 75 mg/m^2/day 6-mercaptopurine (dose other chemotherapeutic regimens not mentioned) *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose: nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: aminotransferases, liver biopsy (n=10) (frequency of testing nm) Definition of hepatic late adverse effects: elevated aminotransferases *N* of patients hepatic late adverse effects at end of follow-up: aminotransferases: 6/43 (14.0%); liver biopsy: 10/10 (100%) portal fibrosis or nodular regenerative hyperplasia Risk factors: not evaluated
Notes	

Risk of bias	***Risk of bias***

Vora 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	High risk	Number of patients with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Weber 1987

Methods	Prospective cohort study (originally developed as a RCT; a selected group of patients was followed up for hepatic late adverse effects)
Participants	*N* of patients original cohort: nm; *N* of patients described study group: 19; *N* of patients study group of interest: 19; *N* of patients with liver function tests: 19 Tumour: ALL; Time period diagnosis/treatment: 1979-1981; Age at diagnosis: range 0.7-17.0 yr [a]; Age at follow-up: nm; F/M%: 47/53[a]; BMI: nm *N* of patients hepatitis virus infection: nm *N* of patients acute liver disease: 19/19 (100%) elevated ALT after 6 courses of high-dose methotrexate Follow-up duration: range 1.0-4.0 yr after end of treatment; Completion of follow-up: 100%
Interventions	*N* of patients chemotherapy: 19/19 (100%); Chemotherapy type: vincristine, L-asparaginase, daunomycin, methotrexate, prednisone, leucovorin, 6-mercaptopurine and cyclophosphamide; Chemotherapy dose: A priming dose of methotrexate, 6000mg/m^2 was administered over 1 hour followed immediately by constant infusion of methotrexate, 1200 mg/m^2/hour for 23 hours. The total dose of methotrexate per course was 33,600 mg/m^2 over 24 hours. Twelve hours after completion of the methotrexate infusion, 200 mg/m^2 leucovorin was administered over 1 hour. Three hours later, leucovorin was started at doses of 12 mg/m^2 every 3 hours for 5 doses, then every 6 hours until the serum methotrexate level fell below 1x10^{-7} M. Six 23-week cycles of prednisone, vincristine, 6-mercaptopurine, L-asparaginase, cyclophosphamide, daunomycin, and twice weekly methotrexate (7.5 mg/m^2 during weeks 3 to 6, 10 to 13, and 17 to 20) were administered. Also high-dose 6-mercaptopurine (500 mg/m^2/day) on days 1 to 5 of each maintenance cycle was received *N* of patients radiotherapy involving the liver: nm; Radiotherapy field: nm; Radiotherapy dose:

Weber 1987 (*Continued*)

	nm *N* of patients hepatectomy: nm *N* of patients BMT: nm *N* of patients blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, bilirubin, ALP (frequency of testing nm) Definition of hepatic late adverse effects: > upper limits of normal: ALT 40 IU/L, total bilirubin 0.8 mg/dL, direct bilirubin 0.3 mg/dL, ALP 180 IU/L (1 yr of age until adolescence), 260 IU/L (adolescent females), 350 IU/L (adolescent males) *N* of patients hepatic late adverse effects at end of follow-up: 0/19 (0.0%) Risk factors: not evaluated
Notes	[a] Data of 36 patients with ALL

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if outcome assessors were blinded to the investigated determinant
Well defined study group	High risk	Number of patients with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

ALL, acute lymphoblastic leukaemia; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AML, acute myeloid leukaemia; ANLL, acute non-lymphoblastic leukaemia; AST, aspartate aminotransferase; BMI, body mass index; BMT, bone marrow transplantation; CML, chronic myeloid leukaemia; GGT, gamma-glutamyl transferase; GVHD, graft-versus-host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HL, Hodgkin lymphoma; HSCT, haematopoietic stem cell transplantation; JCML, juvenile chronic myeloid leukaemia; JMML, juvenile myelomonocytic leukaemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; nm, not mentioned; ns, not significant; PTT, prothrombin time; RAEB, refractory anaemia with blast excess; RCT, randomised controlled trial; RIBA, recombinant immunoblotting assay; SAA, severe aplastic anaemia; TAI, thoraco-abdominal irradiation; TBI, total body irradiation; uc, unclear; VOD, veno-occlusive disease.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adson 1981	Less than 50% aged 18 years or younger
Al-Attar 1986	Not reporting on hepatic late adverse effects
Amylon 1997	Follow-up duration unclear
Atay 2005	Not reporting on hepatic late adverse effects
Avet Loiseau 1991	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Bacigalupo 1991	Not reporting on hepatic late adverse effects
Balcerska 2000	Follow-up duration unclear
Bauditz 2007	Case series
Benesch 2001	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Berjian 1980	No childhood cancer survivors: adult patients >18 years
Berman 1980	Less than 50% aged 18 years or younger
Bernstein 1993	Not reporting on hepatic late adverse effects
Blum 2002	Not reporting on hepatic late adverse effects
Broxson 2005	Case series
Brunet 2001	Less than 50% aged 18 years or younger
Carter 1997	Cancer treatment unclear
Cassady 1979	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Cavo 1998	No childhood cancer survivors: adult patients >18 years
Cesaro 1997	Liver function testing in hepatitis virus positive patients
Chao 1993	Less than 50% aged 18 years or younger
Cheng 2005	No childhood cancer survivors: adult patients >18 years
Cheuk 2008	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)

(*Continued*)

Chou 1996	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Christosova 2005	Case series
Claviez 1996	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Colsky 1955	Case series
Condren 2005	Impossible to differentiate between patients with and without potentially high-risk treatment for hepatic late adverse effects
Damon 2006	No childhood cancer survivors: adult patients >18 years
Deeg 1986	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Dibenedetto 1994	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Dunkel 1998	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Dupuis-Girod 1996	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Evans 1980	Not reporting on hepatic late adverse effects
Evans 1982	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Evans 1990	Less than 50% aged 18 years or younger
Evans 1993	Less than 50% aged 18 years or younger
Exelby 1975	Follow-up duration unclear
Fabbri 1994	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Farthing 1982	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Fink 1993	Impossible to differentiate between patients with and without potentially high-risk treatment for hepatic late adverse effects
Forbes 1995	Less than 50% aged 18 years or younger
Frickhofen 1994	Less than 50% aged 18 years or younger
Gandola 2009	Not reporting on hepatic late adverse effects
Ganjoo 2006	No childhood cancer survivors: adult patients >18 years
Glick 2000	Less than 10 childhood cancer survivors

(*Continued*)

Gluckman 1979	Unclear if one of our defined outcome measures was tested
Gonzalez-Crussi 1982	Not reporting on hepatic late adverse effects
Greenfield 2006	Not reporting on hepatic late adverse effects
Grill 1996	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Grosfeld 1976	Case series
Gutjahr 1980	Cancer treatment unclear
Haddy 1998	Liver function testing in hepatitis virus positive patients
Hadley 2002	Not reporting on hepatic late adverse effects
Halonen 2003	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Hanks 1980	Not reporting on hepatic late adverse effects
Harrison 1996	Less than 50% aged 18 years or younger
Hatanaka 1994	No childhood cancer survivors: adult patients >18 years
Haupt 2004	Unclear if one of our defined outcome measures was tested
Hedrick 2004	Not reporting on hepatic late adverse effects
Hegewald 1982	Not reporting on hepatic late adverse effects according to our defined outcome measures; Unclear if case series or cohort study
Henderson 2008	Case report
Hjern 2007	Not reporting on hepatic late adverse effects
Ho 2004	No childhood cancer survivors: adult patients
Hollard 1980	Less than 50% aged 18 years or younger
Holschneider 1977	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Horowitz 1993	Not reporting on hepatic late adverse effects
Hutter 1960	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Ingold 1965	Case series

(*Continued*)

Isaacs 2008	Not reporting on hepatic late adverse effects
Ivantes 2004	No childhood cancer survivors: adult patients
Jaffe 1975	Review
Jagannathan 2004	No childhood cancer survivors: adult patients >18 years
Jirtle 1990	Review
Kamani 1996	Unclear if one of our defined outcome measures was tested
Kamble 2006	Review
Kaste 1999	Not reporting on hepatic late adverse effects
Kazanowska 2004	Not reporting on hepatic late adverse effects
Khouri 2002	No childhood cancer survivors: adult patients >18 years
Kim 2000	No childhood cancer survivors: adult patients
Kotz 1982	Case series
Kremens 2002	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Kudo 1996	No childhood cancer survivors
Lackner 2000	Impossible to differentiate between patients with and without potentially high-risk treatment for hepatic late adverse effects
Lackner 2007	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Ladenstein 1997	Not reporting on hepatic late adverse effects
Leonardi 2003	Cancer treatment unclear
Leung 2000	Liver function testing in hepatitis virus positive patients
Levitt 2004	Not reporting on hepatic late adverse effects according to our defined outcome measures
Ljungman 1995	Less than 50% aged 18 years or younger
Locasciulli 1989	Less than 50% aged 18 years or younger
Locasciulli 1990a	Age of the patients unclear

(*Continued*)

Locasciulli 1990b	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Locasciulli 1991b	Less than 50% aged 18 years or younger
Locasciulli 1993	Liver function testing in hepatitis virus positive patients
Locasciulli 1995	Review
Maggiore 1982	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Maguire 2002	Not reporting on hepatic late adverse effects
Martinez 1997	No childhood cancer survivors: adult patients >18 years
Masera 1981	Liver function testing in hepatitis virus positive patients
McBride 1976	Less than 50% aged 18 years or younger
McIntosh 1977	Less than 10 childhood cancer survivors
McKay 1996	Less than 50% aged 18 years or younger
Meadows 1992	Unclear if one of our defined outcome measures was tested
Mitrou 1990	Not reporting on hepatic late adverse effects
Moore 1995	Not reporting on hepatic late adverse effects
Morrow 1982	Not reporting on hepatic late adverse effects
Murthy 1978	Not reporting on hepatic late adverse effects
Myers 1995	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection; Information on liver function reported for only 1 patient
Nagasue 1979	No childhood cancer survivors: adult patients >18 years
Nagatoshi 1997	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Neilson 1996	Age of the patients and cancer treatment unclear
O'Hara 1968	Not reporting on hepatic late adverse effects
Oeffinger 2006	Not reporting on hepatic late adverse effects
Osborne 1980	No childhood cancer survivors: adult patients >18 years

(*Continued*)

Pantoja 1975	No childhood cancer survivors: adult patients >18 years
Pao 1989	Not reporting on hepatic late adverse effects
Park 2002	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Poussin-Rosillo 1976	Less than 50% aged 18 years or younger
Pratt 1977	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Pritchard 2005	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Pui 1992	Not reporting on hepatic late adverse effects
Punyko 2005	Not reporting on hepatic late adverse effects
Puri 2006	Not reporting on hepatic late adverse effects
Ravikumara 2006	Less than 50% off treatment for 1 year or more
Reaman 1985	Not reporting on hepatic late adverse effects
Rodriguez-Inigo 1997	No childhood cancer survivors: adult patients
Rossetti 1992	Number of patients with liver function testing unclear; Liver biopsy during first year after chemotherapy (<1 year off treatment)
Samuelsson 1999	Not reporting on hepatic late adverse effects
Sawamura 1998	Not reporting on hepatic late adverse effects
Schaison 1980	Number of patients with liver function testing unclear
Sekine 1998	Number of patients with liver function testing unclear
Sevinir 2003	Liver function testing in hepatitis virus positive patients
Shah 2004	Not reporting on hepatic late adverse effects
Silverman 1997	Not reporting on hepatic late adverse effects
Skidmore 1997	No childhood cancer survivors: adult patients
Socié 1999	Less than 50% aged 18 years or younger
Socié 2001	Not reporting on hepatic late adverse effects

(*Continued*)

Spunberg 1981	Not reporting on hepatic late adverse effects
Strasser 1999a	Less than 50% aged 18 years or younger
Strasser 1999b	Less than 50% aged 18 years or younger
Straus 1991	Not reporting on hepatic late adverse effects
Tada 1997	Liver function testing in hepatitis virus positive patients
Taylor 1997	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Tefft 1977	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Thomas 1988	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Tomás 2000	Less than 50% aged 18 years or younger
Tura 1998	No childhood cancer survivors: adult patients
Uchino 1978	Not reporting on hepatic late adverse effects
Uzel 2001	Not reporting on hepatic late adverse effects
Vaidya 2000	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
van den Ouweland 1983	Less than 50% aged 18 years or younger
Veneri 2003	No childhood cancer survivors: adult patients
Vergani 1982	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection; Liver biopsy at cessation of chemotherapy (<1 year off treatment)
von Schweinitz 1994	Not reporting on hepatic late adverse effects
Wasserheit 1995	Less than 50% aged 18 years or younger
Weirich 2004	Unclear if one of our defined outcome measures was tested
Wexler 1996	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Willers 2001	Liver function testing in hepatitis virus positive patients
Wolff 2006	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Woolfrey 1998	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)

(*Continued*)

Yamada-Osaki 1999	Liver function testing in hepatitis virus positive patients
Yang 2005	Not reporting on hepatic late adverse effects
Yang 2006	Not reporting on hepatic late adverse effects
Zimmermann 2002	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Zittoun 1985	Less than 50% aged 18 years or younger

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kovacs 2007

Methods	Cohort study.
Participants	138 children (78 boys, 60 girls) aged 1-18 years (mean 7.7) with acute leukaemia and non-Hodgkin lymphoma
Interventions	Patients were treated with chemotherapy. Specific details on cancer treatment are not reported
Outcomes	12.1% had elevated ALT and 3.0% elevated GGT at a follow-up of 1-4 years after the end of treatment. 8.2% had elevated ALT and 0.0% elevated GGT at a follow-up >5 years after the end of treatment
Notes	This study has not been published in full text (as of February 2010), but has been presented at the SIOP conference 2007 (abstract PL.004). From currently available data it is unclear if this study is eligible for inclusion in this review

Kristinsson 2002

Methods	Cohort study
Participants	20 childhood cancer survivors treated for leukaemia. Age at diagnosis ranged from 0.4 to 13.8 years, mean age at follow-up was 16.7 years and mean time since end of treatment was 8.3
Interventions	Patients were treated with chemotherapy (n=20), BMT (n=3) and TBI (n=1)
Outcomes	1 patient (5.0%) had elevated GGT and 1 patient (5.0%) had elevated GGT and AST as well
Notes	This study is written in Icelandic. At this moment we are awaiting the translation

Thavaraj 2006

Methods	Cohort study.
Participants	200 paediatric cancer survivors (165 boys, 35 girls) aged 1.3-30 years (mean 9.5) at follow-up with various tumours
Interventions	52 patients were treated with radiotherapy. Specific details on cancer treatment are not reported
Outcomes	14 patients had chronic liver disease and were HBsAntigen^{+} at a median follow-up of 2.5 years.
Notes	This study has not been published in full text (as of February 2010), but has been presented at the SIOP conference 2006 (abstract PJ.032). From currently available data it is unclear if this study is eligible for inclusion in this review

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMT, bone marrow transplantation; GGT, gamma-glutamyl transferase; TBI, total body irradiation.

DATA AND ANALYSES

Comparison 1. Prevalence of hepatic late adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above upper limit of normal	5		Prevalence (Random, 95% CI)	Totals not selected
2 Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above twice upper limit of normal	3		Prevalence (Random, 95% CI)	Totals not selected

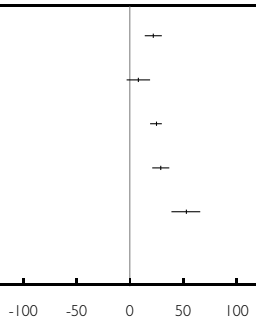
Analysis 1.1. Comparison 1 Prevalence of hepatic late adverse effects, Outcome 1 Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above upper limit of normal.

Review: Hepatic late adverse effects after antineoplastic treatment for childhood cancer

Comparison: 1 Prevalence of hepatic late adverse effects

Outcome: 1 Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above upper limit of normal

Study or subgroup	N	N	Prevalence (SE)	Prevalence IV,Random,95% CI	Prevalence IV,Random,95% CI
Aric 1994	122	0	21.6 (4.07)		21.60 [13.62, 29.58]
Bessho 1994	25	0	8 (5.42)		8.00 [-2.62, 18.62]
Bresters 2008	216	0	24.5 (2.93)		24.50 [18.76, 30.24]
Locasciulli 1997a	114	0	28.9 (4.25)		28.90 [20.57, 37.23]
Locasciulli 1997b	53	0	52.8 (6.86)		52.80 [39.35, 66.25]



Analysis 1.2. Comparison 1 Prevalence of hepatic late adverse effects, Outcome 2 Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above twice upper limit of normal.

Review: Hepatic late adverse effects after antineoplastic treatment for childhood cancer

Comparison: 1 Prevalence of hepatic late adverse effects

Outcome: 2 Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above twice upper limit of normal

Study or subgroup	N	N	Prevalence (SE)	Prevalence IV,Random,95% CI	Prevalence IV,Random,95% CI
Bresters 2008	216	0	7.9 (1.84)		7.90 [4.29, 11.51]
Ratner 1986	39	0	23.1 (6.75)		23.10 [9.87, 36.33]
Rossetti 1991	96	0	44.8 (5.08)		44.80 [34.84, 54.76]

ADDITIONAL TABLES

Table 1. Risk of bias assessment criteria for observational studies

	Internal validity	External validity
Study group	Selection bias (representative: yes/no) • if the described study group consisted of more than 90% of the original cohort of childhood cancer survivors • *or* if it was a random sample with respect to the cancer treatment	Reporting bias (well defined: yes/no) • if the type of chemotherapy and/or location of radiotherapy was mentioned • *and* if the number of patients with chronic viral hepatitis was mentioned
Follow-up	Attrition bias (adequate: yes/no) • if the outcome was assessed for more than 90% of the study group of interest (++) • *or* if the outcome was assessed for 60-90% of the study group of interest (+)	Reporting bias (well defined: yes/no) • if the length of follow-up was mentioned
Outcome	Detection bias (blind: yes/no) • if the outcome assessors were blinded to the investigated determinant	Reporting bias (well defined: yes/no) • if the outcome definition was objective and precise, i.e. if the upper limits of normal for liver function tests were described in the definition of hepatic late adverse effects
Risk estimation	Confounding (adjustment for other factors: yes/no) • if important prognostic factors (i.e. age, gender, co-treatment) or follow-up were taken adequately into account	Analyses (well defined: yes/no) • if a relative risk, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi^2 was calculated

Table 2. Risk factors from univariate analyses that increase the risk of hepatic late adverse effects

Study	Risk factor	Significant (+/-)
Aricò 1994	Chronic HCV infection	+
Ballauf 1999	Chronic HCV and HBV infection	+
Bresters 2008	Older age at HSCT	+
Bresters 2008	Diagnosis of benign haematological disease	+
Bresters 2008	Gender	-
Bresters 2008	HSCT donor type (matched sibling donor, other)	-
Bresters 2008	Haematopoietic stem cell source (bone marrow, autologous peripheral blood, cord blood)	-
Bresters 2008	Conditioning regimen (cyclophosphamide with TBI/TAI, cyclophosphamide with busulphan, other)	-
Bresters 2008	Early post-transplant morbidity (viral reactivation, VOD, acute GVHD)	-
Chotsampancharoen 2009	Iron overload (high serum ferritin)	+
Locasciulli 1983	Cleared or persistent chronic HBV infection	+
Locasciulli 1983	Histological diagnosis of chronic hepatitis	+
Locasciulli 1991a	Chronic HCV infection	+
Locasciulli 1997a	Chronic HCV infection	+
Rossetti 1991	Chronic HBV-HDV co-infection	+
Rossetti 1991	Chronic HBV infection	+
Tefft 1970	Site of radiotherapy (right lobe, left lobe, entire liver, remaining liver)	-
Tefft 1970	Radiotherapy dose (<25 Gy, 25-35 Gy, >35 Gy)	-

+, significant; -, not significant; GVHD, graft-versus-host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HSCT, haematopoietic stem cell transplantation; VOD, veno-occlusive disease.

APPENDICES

Appendix 1. Search strategy for MEDLINE (PubMed)

1. For **hepatic late adverse effects** the following MeSH headings and text words were used:
(liver fibrosis) OR (liver cirrhosis) OR (liver disease OR liver diseases OR liver diseas*) OR (liver dysfunction OR liver dysfunctions) OR (liver damage) OR (liver failure) OR (liver enzyme[all fields] OR liver enzymes[all fields] OR (liver enzym*) OR (liver toxicity) OR (liver disfunction) OR (radiation-induced liver disease OR radiation induced liver disease OR RILD) OR (liver function test OR liver function tests) OR (liver insufficiency) OR (Hepatic Cirrhosis OR Cirrhoses, Hepatic OR Cirrhosis, Hepatic OR Hepatic Cirrhoses OR Cirrhosis, Liver OR Cirrhoses, Liver OR Liver Cirrhoses OR Fibrosis, Liver OR Fibroses, Liver OR Liver Fibroses) OR (Disease, Liver OR Diseases, Liver OR Dysfunction, Liver OR Dysfunctions, Liver OR Liver Dysfunctions) OR (Function Test, Liver OR Function Tests, Liver OR Liver Function Test OR Test, Liver Function OR Tests, Liver Function) OR (Insufficiency, Hepatic OR Liver Insufficiency OR Insufficiency, Liver) OR (hepatic dysfunction) OR (hepatic dysfunctions) OR (hepatic cirrhosis) OR (hepatic failure) OR (hepatic function[all fields]) OR (liver function[all fields]) OR (radiation hepatitis) OR (hepatitis irradiation) OR (impaired liver function) OR (hepatic fibrosis OR hepatic fibroses) OR (drug induced hepatitis) OR (toxic hepatitis) OR (hepatitides) OR (ASAT OR ALAT OR SGPT OR SGOT OR GGT) OR (alanine transaminase OR Transaminase, Alanine OR Glutamic-Alanine Transaminase OR Glutamic Alanine Transaminase OR Transaminase, Glutamic-Alanine OR Alanine-2-Oxoglutarate OR Aminotransferase OR Alanine 2 Oxoglutarate Aminotransferase OR Aminotransferase, Alanine-2-Oxoglutarate OR Alanine Aminotransferase OR Aminotransferase, Alanine OR Glutamic-Pyruvic Transaminase OR Glutamic Pyruvic Transaminase OR Transaminase, Glutamic-Pyruvic) OR (gamma Glutamyltransferase OR Glutamyl Transpeptidase OR Transpeptidase, Glutamyl OR GGTP OR gamma-Glutamyl Transpeptidase OR Transpeptidase, gamma-Glutamyl OR gamma Glutamyl Transpeptidase OR gammaglutamyltransferase) OR (Aspartate Aminotransferases OR Aminotransferases, Aspartate OR Aspartate Apoaminotransferase OR Apoaminotransferase, Aspartate OR Aspartate Transaminase OR Transaminase, Aspartate OR Glutamic-Oxaloacetic Transaminase OR Glutamic Oxaloacetic Transaminase OR Transaminase, Glutamic-Oxaloacetic OR L-Aspartate-2-Oxoglutarate Aminotransferase OR Aminotransferase, L-Aspartate-2-Oxoglutarate OR L Aspartate 2 Oxoglutarate Aminotransferase OR Aspartate Aminotransferase OR Aminotransferase, Aspartate OR Glutamate-Aspartate Transaminase OR Glutamate Aspartate Transaminase OR Transaminase, Glutamate-Aspartate OR Serum Glutamic-Oxaloacetic Transaminase OR Glutamic-Oxaloacetic Transaminase, Serum OR Serum Glutamic Oxaloacetic Transaminase OR Transaminase, Serum Glutamic-Oxaloacetic) OR (hepatotoxicity OR hepatotoxic OR hepatotoxic*) OR (Veno-occlusive disease OR VOD) OR (Veno occlusive disease) OR (hepatic veno-occlusive disease OR Disease, Hepatic Veno-Occlusive OR Hepatic Veno-Occlusive Diseases OR Sinusoidal Obstruction Syndrome OR Syndrome, Sinusoidal Obstruction OR Hepatic Veno Occlusive Disease OR Veno-Occlusive Disease, Hepatic OR Veno Occlusive Disease, Hepatic) OR (iron overload OR hemosiderosis OR siderosis OR heamosiderosis OR haemosiderosis) OR (Hemosideroses OR Overload, Iron) OR (bilirubin OR bilirubins OR bilirubin* OR Bilirubin IX alpha OR Bilirubin, (4E)-Isomer OR Bilirubin, (4E,15E)-Isomer OR Hematoidin OR Bilirubin, Disodium Salt OR Disodium Salt Bilirubin OR Bilirubin, Monosodium Salt OR Monosodium Salt Bilirubin OR delta-Bilirubin OR delta Bilirubin OR Bilirubin, (15E)-Isomer OR Bilirubin, Calcium Salt OR Calcium Salt Bilirubin OR Salt Bilirubin, Calcium OR Calcium Bilirubinate OR Bilirubinate, Calcium) OR (albumin OR albumins OR albumin*) OR (prothrombin OR prothrombins OR prothrombin*) OR (Factor II OR Blood Coagulation Factor II OR Differentiation Reversal Factor OR Factor, Differentiation Reversal OR Coagulation Factor II OR Factor II, Coagulation OR II, Coagulation Factor) OR (Alkaline phosphatase)
2. For **survivors** the following MeSH headings and text words were used:
Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR Survivor, Long-Term OR Survivors, Long-Term OR survivo* OR surviving
3. For **childhood cancer** the following MeSH headings and text words were used:
(((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology)) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia lymphocytic acute) OR (leukemia, lymphocytic, acute[mh])
The different searches were combined as **1** AND **2** AND **3**.
[* = zero or more characters; mh = MeSH term]

Appendix 2. Search strategy for EMBASE (Ovid)

1. For **Hepatic late adverse effects** the following Emtree terms and text words were used:
1. liver fibrosis.mp. or exp Liver Fibrosis/
2. (liver disease or liver diseases or liver diseas$).mp. or exp Liver Disease/
3. (liver dysfunction or liver dysfunctions or liver disfunction).mp. or exp Liver Dysfunction/
4. (hepatic dysfunction or hepatic dysfunctions or hepatic dysfunction$).mp.
5. (liver cirrhosis or liver cirrhoses).mp. or exp Liver Cirrhosis/
6. (hepatic cirrhosis or hepatic cirrhoses).mp.
7. (liver fibroses or hepatic fibrosis or hepatic fibroses).mp.
8. (liver damage or liver insufficiency or impaired liver function or hepatic insufficiency).mp.
9. exp Radiation Injury/ or (radiation induced liver disease or radiation-induced liver disease or RILD).mp.
10. (radiation hepatitis or hepatitis irradiation).mp.
11. drug induced hepatitis.mp. or exp Toxic Hepatitis/ or toxic hepatitis.mp. or hepatitides.mp.
12. liver failure.mp. or exp Liver Failure/
13. hepatic failure.mp.
14. liver enzyme.mp. or exp Liver Enzyme/
15. (liver enzymes or liver enzym$).mp.
16. hepatic function.mp. or exp Liver Function/
17. (liver function test or liver function tests.mp. or exp Liver Function Test/
18. liver toxicity.mp. or exp Liver Toxicity/
19. (hepatotoxicity or hepatotoxic or hepatotoxic$).mp.
20. (ASAT or ALAT or SGPT or SGOT or GGT).mp.
21. (Glutamic-Alanine Transaminase or Glutamic Alanine Transaminase).mp.
22. gamma Glutamyltransferase.mp. or exp Gamma Glutamyltransferase/
23. (Glutamyl Transpeptidase or GGTP or gamma-Glutamyl Transpeptidase or gamma Glutamyl Transpeptidase or gammaglutamyl-transferase).mp.
24. (Alanine-2-Oxoglutarate or alanine transaminase).mp. or exp Alanine Aminotransferase/
25. (aspartate aminotransferases or aspartate aminotransferase).mp. or exp aspartate aminotransferase/
26. (aspartate apoaminotransferase or aspartate transaminase or glutamic-oxaloacetic transaminase or glutamic oxaloacetic transaminase or L-aspartate-2-oxoglutarate aminotransferase or L aspartate 2 oxoglutarate aminotransferase or glutamate-aspartate transaminase or glutamate aspartate transaminase).mp.
27. (Aminotransferase or Alanine 2 Oxoglutarate Aminotransferase).mp.
28. (alanine aminotransferase or serum glutamic-oxaloacetic transaminase or serum glutamic oxaloacetic transaminase).mp. or exp Aspartate Aminotransferase Blood Level/
29. (Glutamic-Pyruvic Transaminase or Glutamic Pyruvic Transaminase).mp.
30. (veno-occlusive disease or veno occlusive disease).mp. or exp vein occlusion/
31. (VOD or hepatic veno-occlusive disease or hepatic veno-occlusive diseases or hepatic venoocclusive disease).mp. or exp Liver Vein Obstruction/
32. sinusoidal obstruction syndrome.mp.
33. Iron overload.mp. or exp Iron Overload/
34. (hemosiderosis or siderosis or heamosiderosis or haemosiderosis or hemosideroses).mp. or exp Liver Hemosiderosis/ or exp siderosis/
35. (bilirubin or bilirubins or bilirubin$ or bilirubin IX alpha or hematoidin or disodium salt bilirubin or monosodium salt bilirubin or delta-bilirubin or delta bilirubin or calcium salt bilirubin or calcium bilirubinate).mp. or exp Bilirubin/
36. (albumin or albumins or albumin$).mp. or exp Albumin/
37. exp Prothrombin/ or (prothrombin or prothrombins or prothrombin$ or factor II or blood coagulation factor II or differentiation reversal factor or coagulation factor II).mp.
38. Alkaline phosphatase.mp. or exp Alkaline Phosphatase/
39. or/1-38

2. For**Survivors** the following Emtree terms and text words were used:
1. (survivor or survivors or (long adj term survivor) or (long adj term survivors) or survivo$).mp.
2. survivor/ or cancer survivor/
3. surviving.mp.

4. 1 or 2 or 3

3. For **Childhood cancer** the following Emtree terms and text words were used:

1. (leukemia or leukemi$ or leukaemi$ or (childhood adj ALL) or acute lymphocytic leukemia).mp.
2. (AML or lymphoma or lymphom$ or hodgkin or hodgkin$ or T-cell or B-cell or non-hodgkin).mp.
3. (sarcoma or sarcom$ or Ewing$ or osteosarcoma or osteosarcom$ or wilms tumor or wilms$).mp.
4. (nephroblastom$ or neuroblastoma or neuroblastom$ or rhabdomyosarcoma or rhabdomyosarcom$ or teratoma or teratom$ or hepatoma or hepatom$ or hepatoblastoma or hepatoblastom$).mp.
5. (PNET or medulloblastoma or medulloblastom$ or PNET$ or neuroectodermal tumors or primitive neuroectodermal tumor$ or retinoblastoma or retinoblastom$ or meningioma or meningiom$ or glioma or gliom$).mp.
6. (pediatric oncology or paediatric oncology).mp.
7. ((childhood adj cancer) or (childhood adj tumor) or (childhood adj tumors) or childhood malignancy or (childhood adj malignancies) or childhood neoplasm$).mp.
8. ((pediatric adj malignancy) or (pediatric adj malignancies) or (paediatric adj malignancy) or (paediatric adj malignancies)).mp.
9. ((brain adj tumor$) or (brain adj tumour$) or (brain adj neoplasms) or (brain adj cancer$) or brain neoplasm$).mp.
10. (central nervous system tumor$ or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumour$).mp.
11. intracranial neoplasm$.mp.
12. LEUKEMIA/ or LYMPHOMA/ or brain tumor/ or central nervous system tumor/ or teratoma/ or sarcoma/ or osteosarcoma/
13. nephroblastoma/ or neuroblastoma/ or rhabdomyosarcoma/ or hepatoblastoma/ or medulloblastoma/ or neuroectodermal tumor/ or retinoblastoma/ or meningioma/ or glioma/ or childhood cancer/
14. or/1-13

The different searches were combined as **1** AND **2** AND **3**.

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; / = Emtree term; $ = zero or more characters]

Appendix 3. Search strategy for CENTRAL

1. For **Hepatic late adverse effects** the following text words were used:

(liver fibrosis OR liver cirrhosis OR liver disease OR liver diseases OR liver diseas* OR liver dysfunction OR liver dysfunctions OR liver damage OR liver failure OR liver enzyme OR liver enzymes OR liver enzym* OR liver toxicity OR liver disfunction OR radiation-induced liver disease OR radiation induced liver disease OR RILD OR liver function test OR liver function tests OR liver insufficiency OR Hepatic Cirrhosis OR hepatic dysfunction OR hepatic dysfunctions OR hepatic cirrhosis OR hepatic failure OR hepatic function OR liver function OR radiation hepatitis OR hepatitis irradiation OR impaired liver function OR hepatic fibrosis OR hepatic fibroses OR drug induced hepatitis OR toxic hepatitis OR hepatitides OR ASAT OR ALAT OR SGPT OR SGOT OR GGT OR alanine transaminase Glutamic-Alanine Transaminase OR Glutamic Alanine Transaminase OR Alanine-2-Oxoglutarate OR Aminotransferase OR Alanine 2 Oxoglutarate Aminotransferase OR Alanine Aminotransferase OR Glutamic-Pyruvic Transaminase OR Glutamic Pyruvic Transaminase OR gamma Glutamyltransferase OR Glutamyl Transpeptidase OR GGTP OR gamma-Glutamyl Transpeptidase OR gamma Glutamyl Transpeptidase OR gammaglutamyltransferase OR Aspartate Aminotransferases OR Aspartate Apoaminotransferase OR Aspartate Transaminase OR Glutamic-Oxaloacetic Transaminase OR Glutamic Oxaloacetic Transaminase OR L-Aspartate-2-Oxoglutarate Aminotransferase OR L Aspartate 2 Oxoglutarate Aminotransferase OR Aspartate Aminotransferase OR Glutamate-Aspartate Transaminase OR Glutamate Aspartate Transaminase OR Serum Glutamic-Oxaloacetic Transaminase OR Serum Glutamic Oxaloacetic Transaminase OR hepatotoxicity OR hepatotoxic OR hepatotoxic* OR Veno-occlusive disease OR VOD OR Veno occlusive disease OR hepatic veno-occlusive disease OR Hepatic Veno-Occlusive Diseases OR Sinusoidal Obstruction Syndrome OR Hepatic Veno Occlusive Disease OR iron overload OR hemosiderosis OR siderosis OR heamosiderosis OR haemosiderosis OR Hemosideroses OR bilirubin OR bilirubins OR bilirubin* OR Bilirubin IX alpha OR Hematoidin OR Disodium Salt Bilirubin OR Monosodium Salt Bilirubin OR delta-Bilirubin OR delta Bilirubin OR Calcium Salt Bilirubin OR Calcium Bilirubinate OR albumin OR albumins OR albumin* OR prothrombin OR prothrombins OR prothrombin* OR Factor II OR Blood Coagulation Factor II OR Differentiation Reversal Factor OR Coagulation Factor II OR Alkaline phosphatase)

2. For **Survivors** the following text words were used:

(Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR survivo* OR surviving)

3. For **Childhood cancer** the following text words were used:

(leukemia OR leukemi* OR leukaemi* OR childhood ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm OR acute lymphocytic leukemia)
The different searches were combined as **1** AND **2** AND **3**.
The search will be performed in title, abstract or keywords.
[* =zero or more characters]

WHAT'S NEW

Last assessed as up-to-date: 21 December 2009.

Date	Event	Description
29 January 2015	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Renée Mulder designed the study and wrote the protocol. She identified the studies meeting the inclusion criteria (both by initial screening and thereafter). She searched for unpublished and ongoing studies; performed the data extraction and the risk of bias assessment of the included studies; analysed the data and interpreted the results. She wrote and revised the manuscript.

Elvira van Dalen designed the study and critically reviewed the protocol. She identified studies meeting the inclusion criteria and contributed to the interpretation of the results. She critically reviewed the manuscript.

Malon Van den Hof performed the data extraction and the risk of bias assessment of the included studies. She analysed the data and interpreted the results.

Dorine Bresters critically reviewed the protocol. She identified studies meeting the inclusion criteria. She critically reviewed the manuscript.

Bart Koot critically reviewed the protocol. He identified studies meeting the inclusion criteria and contributed to the interpretation of the results. He critically reviewed the manuscript.

Sharon Castellino critically reviewed the manuscript.

Yoon Loke critically reviewed the protocol and the manuscript.

Edith Leclercq developed the search strategy. She critically reviewed the protocol and identified studies meeting the inclusion criteria. She critically reviewed the manuscript.

Piet Post critically reviewed the protocol. He identified studies meeting the inclusion criteria. He critically reviewed the manuscript.

Huib Caron critically reviewed the protocol and the manuscript.

Aleida Postma critically reviewed the protocol. She identified studies meeting the inclusion criteria. She critically reviewed the manuscript.

Leontien Kremer designed the study and critically reviewed the protocol. She identified studies meeting the inclusion criteria and contributed to the interpretation of the results. She critically reviewed the manuscript.

All authors approved the final version.

DECLARATIONS OF INTEREST

Dorine Bresters is an author of a study included in this systematic review.

SOURCES OF SUPPORT

Internal sources

- Dutch Cochrane Centre, Netherlands.

External sources

- Foundation of Paediatric Cancer Research (SKK), Netherlands.
- Stichting Kinderen Kankervrij (KiKa), Netherlands.
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of this systematic review. The title of the protocol was 'Hepatic late adverse effects after treatment for childhood cancer'. The new title is 'Hepatic late adverse effects after antineoplastic treatment for childhood cancer'.

In the protocol it was stated that all study designs, except case reports and case series, examining the effect of treatment for childhood cancer on hepatic late adverse effects would be included. However, we also excluded studies including less than 10 patients.

In addition, in the protocol it was stated that studies with a maximum follow-up of one year or less would be excluded and if no follow-up time after the end of treatment was stated more than 90% of the study group should have been off treatment. However, we decided to only include studies in which more than 50% of the study group was off treatment for at least one year to assure that we would analyse late adverse effects and not acute toxicity.

Also, we adapted the risk of bias assessment criteria for an adequate follow-up and a well defined outcome. The definition of a low risk of follow-up bias was as follows: if the outcome was assessed at the end date of the study for 60% to 90% of the study group or if the outcome was assessed for more than 90% of the study group but with an unknown end date. Since there is not a straightforward definition for the end date of the study, we decided to change this risk of bias item. The new definition of a low risk of follow-up bias is as follows: if the outcome was assessed for more than 90% of the study group of interest (++) or if the outcome was assessed for 60% to 90% of the study group of interest (+). In the protocol we had not yet specified the definition of a well defined outcome. The definition is as follows: if the outcome definition was objective and precise, that is if the upper limits of normal for liver function tests were described in the definition of hepatic late adverse effects.

Since we were able to perform the analysis using RevMan we did not need the statistical software Comprehensive Meta Analysis.

Finally, in the protocol it was stated that we planned to conduct a multivariate linear meta-regression analysis to examine the relation between potential predictive factors and hepatic late adverse effects. Because studies lacked important data on potential predictive factors (that is treatment characteristics, age at diagnosis, age at treatment) we were not able to perform this analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Alanine Transaminase [metabolism]; Antineoplastic Agents [*adverse effects]; Chemical and Drug Induced Liver Injury [*etiology]; Cohort Studies; Hepatitis, Viral, Human [complications]; Liver [drug effects]; Neoplasms [*drug therapy]

MeSH check words

Child; Humans